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VOL. 48, No. 5 NEW SERIES OCTOBER, 1941

# A Discussion on the Origin of Cysts of the Broad Ligament

## WITH A DESCRIPTION OF A BROAD LIGAMENT CYST WHICH, WITH THE FALLOPIAN TUBE AND THE OVARY, HAD UNDERGONE TORSION

BY

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WHEN reading the literature concerning the cystic structures which may be found in the broad ligament one is impressed by the number of articles and case-records which demonstrate a looseness of pathological nomenclature which would not be tolerated in connexion with any other part of the body. That this inadequacy has been recognized by others is indicated in an article written 30 years ago by Keith and Doran,[8] who clearly state that certain cysts which arise in the vicinity of the ovarian fimbria must not any longer be called parovarian. The terms which lend themselves to the creation of confusion of thought are: fimbrial cyst, parovarian cyst, Wolffian cyst, Gartner's duct cyst, and broad ligament cyst. Some authors use these terms synonymously while others refer to specific structures with special properties when they employ them. We shall discuss at some length the relative merits of these terms, and in order to do so more effectively

will first proceed to pass in review the vestigial structures which are to be found in the broad ligament.

## The Vestigial Structures of the Broad Ligament and Mesovarium

For the origin of the vestigial structures which are found in the broad ligament and mesovarium we must turn to embryological investigations on the origin of the genital and nephric systems. Because of their importance in this connexion we shall deal with the development of the genital and nephric systems in detail.

The genital and nephric systems develop in the intermediate cell mass which is found on either side of the mesentery as an elongated body of cells having cephalic and caudal extremities.

The nephric element develops in three phases, namely the pronephros, the mesonephros and the metanephros or permanent kidney.

### *The Pronephros.*

The pronephros originates and disappears, more or less completely, early in embryonic life. It attains its greatest development when the embryo is no more than 4 mm. long. It is estimated that its period of life is about one week, but it is possible for certain parts of its structure to remain in the broad ligament and these may be discovered during adult life.

The pronephros is composed of about 12 tubules which are connected to a duct, known at this stage as the pronephric duct. The anterior end of the duct is formed by the union of these tubules. In the human subject neither the pronephros nor its duct is functional. The latter is not a duct in the strict sense as it is not canalized at this stage of development.

It is the general belief that most, if not all, of the pronephric tubules disappear, but the pronephric duct remains to form part of the next nephric system. At this point it should be remembered that if the pronephric tubules persisted they would take the form of diverticula of the cephalic end of the duct, and if the lumen of any one of them became constricted they would tend to undergo cystic change. The residuary elements of the pronephric system form the hydatid of Morgagni and Kobelt's tubules.

### *The Mesonephros.*

The second kidney or mesonephros starts to develop before the pronephric tubules have disappeared. The kidney derived

from this system is the functional kidney of the fish. Like the pronephros its cephalic extremity starts to degenerate before the posterior part has developed so that, of the total of 83 tubules which are characteristic of the organ, not more than 40 are to be seen at any one moment. Finally, only 26 tubules of its caudal end remain (Dodds[21]): these are very important in the development of the drainage system of the male sex gland, but of less importance in the female. The remains of these are to be found in the broad ligament of the adult; according to anatomical textbooks they form the organ of Rosenmüller (epi-oöphoron) and the paroöphoron (Figs. 1 and 3). The tubules of the mesonephros effect a union with the pronephric duct which, from this time onwards, is known as the mesonephric or Wolffian duct.

*The Metanephros.*

This forms the permanent kidney of the adult and is developed from the caudal end of the intermediate cell mass. It is of little importance in connexion with the cysts with which this paper deals and will not be further considered.

## The Development of the Sex Glands

The development of the gonads takes place in close proximity to the kidney: their rudiments appear when the embryo is about 5 mm. long (5 weeks), i.e. about the time when the pronephros has disappeared and the mesonephros is developing and is of good size. The epithelium on the medial surface of the mesonephros becomes thicker and constitutes a ridge—the genital ridge. The gonad develops in this. Cellular proliferation causes the ridge to become more prominent. In the course of growth the attachment of the gonad to the mesonephros becomes constricted, in the case of the ovary giving origin to a layer of tissue known as the mesovarium. It is possible for the site of constriction to vary from embryo to embryo, and it follows from this that mesonephric elements may be included in the mesovarium and even in the substance of the ovary.

Cellular proliferation of the genital ridge results in the production of columns of cells called the sex cords: in the female they are not so pronounced as they are in the male.

In the male the sex cords become the testis cords: these eventually unite at the hilum in a special network, the rete testis, which is described lower down. In due course the rete becomes connected with some of the residual mesonephric tubules. The

residual mesonephric tubules which are selected for this purpose are the 5 to 12 tubules placed at the cephalic end of the residual group, estimated as being 26 in number. For this reason they are known as the genital tubules of the mesonephros. It should be noted that they were once functioning as nephric elements and are now destined to become part of the excretory system of the testis. In later development they become very convoluted and form the lobules of the epididymis which together constitute the head of the epididymis. The duct into which they drain, the Wolffian or mesonephric duct, becomes the epididymis and the vas deferens. (See Fig. 1, A, B, C, D, and E.)

The efferent ducts of the testis (vasa efferentia) have thick walls due to the presence of muscular tissue which is principally arranged in a circular direction, and they are lined by ciliated columnar epithelium. It is of importance to notice that the cells of the genital mesonephric tubules are capable of giving origin to ciliated columnar epithelium, especially in connexion with the histology of cysts of the broad ligament and also of the ovary.

It is now necessary to consider the means whereby the testis cords are united with the genital mesonephric tubules.

## The Junction of the Testis Cords with the Genital Mesonephric Tubules

Some controversy exists concerning the method whereby the testis cords are joined to the genital tubules.

The views which are held are as follows:

(1) The union is effected by the development of a separate junctional system, given the name of rete cords or junctional cords (Allen).

(2) The rete is derived directly by the junction of the testis cords where they anastomose in the hilum. This means that the rete is derived from the cords of the genital ridge and represents a continuation of the seminiferous tubules; according to this view they might be expected to have some features in common with the latter.

(3) The rete is derived from outgrowths of the tubules of the mesonephros: in this case they might be expected to bear a resemblance to these mesonephric tubules.

(4) It has also been suggested that they are derived from the capsules of the mesonephric Malpighian corpuscles.

The junctional tubules are in fact lined by a very thin single layer of cells and are not surrounded by muscle.

With regard to the theory of a separate origin of the junctional system, we must bear in mind that the ovary is normally developed from the middle part of the genital ridge, the anterior and posterior parts undergoing atrophic changes. According to Allen[9] (quoted by Keith) the anterior vestigial part develops some solid cords of cells, corresponding to peritoneal funnels, which grow into the mesentery common to the genital and nephric systems. The rete testis is developed from these cords and establishes communication with the seminal tubules (the vasa recti of the testis) on the one hand, and with the blind extremities of the genital tubules of the mesonephros on the other.

*The Junctional System in the Female.*

In the case of the ovary an intrinsic tubular system does not arise and the junctional system has, therefore, nothing with which to unite in the substance of the ovary. However, the junctional tubules may unite with the genital tubules of mesonephric origin. These arrangements are shown diagrammatically in Fig. 2.

According to Keith[9] the fimbriated hydatids (peritoneal funnels) represent some of the remains of the junctional system in the female.

*The Fate of the Wolffian (Mesonephric) Duct.*

It has already been explained that in the male the genital tubules open into the Wolffian (mesonephric) duct which becomes the epididymis and the vas deferens and also forms other accessory male structures. The upper extremity of the duct is indicated by a stalked hydatid which is seen on the upper end of the testicle: this may be regarded as of mesonephric origin, but as the duct is in reality the pronephric duct put to an additional purpose, it may also be regarded as a pronephric structure. In the female a similar small cyst may be seen at the outer end of the Wolffian duct—this is a Kobelt's cyst.

In the female the Wolffian system is overshadowed by the development of the Müllerian ducts; nevertheless mesonephric elements persist. When the ovary migrates into the pelvis the Müllerian duct and Wolffian remnants move with it and start to take up the position characteristic of the adult. This arrangement is seen in Fig. 3.

In the adult female the tube representing the Wolffian duct is seen running parallel to the Fallopian tube and about a quarter of an inch below it. In the mesosalpinx it runs from the region of

the ovarian fimbria in the direction of the uterus. Near the ovarian fimbria (originally the cephalic extremity) the Wolffian duct displays a hydatid (a Kobelt's cyst), which corresponds to a similar structure on the testis. During the 3rd month the duct gradually disappears below the point where it approximates to the side of the developing uterus. Sometimes it persists in its entirety, and when it does so it passes in the walls of the uterus and vagina and finally opens at a depression in the vestibule a little to one side of the external urinary meatus. A Danish anatomist by the name of Gartner[1] described the para-vaginal portion of the Wolffian duct in some of the lower mammalia. It is, therefore, not correct to apply his name to the free and persistent portion of the duct in *homo*. The term "Gartner's duct" should be strictly limited to the persistent duct below the level at which it generally disappears.

In women the genital mesonephric tubules persist and constitute the structure known anatomically as the epoöphoron (epioöphoron, organ of Rosenmüller), while the other residual mesonephric tubules constitute the paroöphoron. In the adult the Wolffian duct exists as a thin tube running below and roughly parallel to the Fallopian tube as far as the uterine wall.

In adult women the paroöphoron tubules are placed between the epoöphoron and the uterus. Some textbooks, e.g. "Ten Teachers", refer to Gartner's duct, Kobelt's tubules, the epoöphoron and paroöphoron by the collective term "parovarium" (as already pointed out the term "Gartner's duct" is incorrectly used in this connexion), and it states that the true parovarian tumours arise from Kobelt's tubules, the epoöphoron and the paroöphoron, most commonly from the vertical tubules and the ducts. We shall examine this statement in greater detail lower down.

According to Cole,[7] the degree of development of the parovarium varies with the age of the subject without direct relation to the increase in size of the broad ligament. The parovarium is difficult to distinguish by the naked eye in the foetus. At 12 years of age it may easily escape notice although the uterus, broad ligament and all the sexual apparatus have considerably increased in size. It is well marked from the age of 20 onwards and is most evident in women between 40 and 53 years of age.

The development of the Müllerian duct is a simpler matter, but there is even now some dispute over the homologies of the distal portion of the Fallopian tube. It is unnecessary further to

consider the development of the Müllerian system, but it is of importance to note that anatomists have described in about 20 per cent of female subjects the presence of a structure which they call an accessory Fallopian tube: this tube is seldom provided with an ostium. Comparative anatomical studies show that the fimbriated end of the Fallopian tube is a derivative of the pronephros, and it is believed by many that the small cysts which are to be found along the ovarian fimbria, including the hydatid of Morgagni which is attached to the ovarian fimbria, are all of pronephric origin.

That portion of the ovary to which the fimbria is attached represents its original cephalic extremity which in the embryo is continued upwards as the diaphragmatic fold. This portion of the ridge is specially remarkable for the number of invaginations which occur in it—the Müllerian duct arises in its anterior end in the form of a modified peritoneal funnel about the 6th week, the tubules of the pronephros have a similar funnel-shaped connexion with the coelomic cavity, and the junctional tubules arise in the same area. Since they are of similar origin it is to be expected that all of these structures may give origin to cysts or tumours of a similar nature. The tubules of the mesonephros are not provided with peritoneal openings and in most features they conform to the characteristics of secretory tubules such as are seen in the permanent kidney.

The arrangement of the three tubular systems which begin as peritoneal invaginations, viz., Wolffian, Müllerian and junctional, are represented diagrammatically in Figs. 1, 2 and 3.

Before we pass on it would be well, for the reasons given below, to recall the nature of the epithelial lining of the adult Fallopian tube.

*The Epithelium of the Fallopian Tube.*

The Fallopian tube consists of three coats, an outer or serous coat composed of peritoneum and a thin layer of connective tissue, a middle coat consisting of an inner circular and an outer longitudinal layer of unstriated muscle and an inner coat consisting of mucous membrane, separated from the middle coat by a basement membrane. The lining epithelium is chiefly of the columnar ciliated variety. The inner surfaces of the fimbriae are also lined by the same type of epithelium; this gradually merges into the endothelium of the peritoneum at their free ends.

The epithelium in the sexually mature woman consists of 3 varieties of cells which rest upon the basement membrane. These cells are known as the ciliated cells, the secretory cells and

the intercalary cells. The cells lining the tube exhibit rhythmic changes in size and shape which go hand in hand with the menstrual cycle. The secretory cells appear to be able to expel their cytoplasm, and in some cases even expel the nucleus.

If a cyst were to arise from this mucous membrane one would expect it to be lined by one or more of these types of cells. The secretion inside the cyst should be the semi-inspissated normal secretion of the secretory cells. If the cyst were large, one might expect the cells to become rather flattened but to retain their specific characters during reproductive life because of their ability to respond to hormonic stimuli.

In women who have passed the menopause the secretory activity is in abeyance and cysts arising at this time would tend to be small, the lining cells flattened and the cilia may be lost, but even in such cases it should be possible to demonstrate cilia in some part of the cyst wall because cilia do not generally disappear from the tubal mucosa with increasing age.

## The Origin of Broad Ligament Cysts

It is clear that cysts in the broad ligament may be derived from:

(1) The pronephric system.
(2) The Wolffian duct and its diverticula, (*a*) Genital tubules (epoöphoron); (*b*) Nephric tubules (paroöphoron).
(3) The Müllerian duct.
(4) The junctional tubules.
(5) Duplications of 1, 2, or 3.
(6) From other structures, e.g. lymphangiomata.

The Müllerian duct gives origin in the greater part of its length to the columnar variety of epithelium (that is, except in that part of it which helps to form the vagina). In the Fallopian tube of the adult many of the epithelial cells are ciliated, but in young persons and the aged the cilia may be absent. The nephrostomes (peritoneal funnels) of the pronephros in the lower animals are provided with long cilia. The duct of the pronephros becomes the Wolffian duct, and this in time becomes the epididymis and vas deferens of the male. These structures also develop ciliated columnar epithelium. One would, therefore, expect the residual genital tubules in the broad ligament, in part at least, to be lined by cells of the same variety. The junctional tubules which form

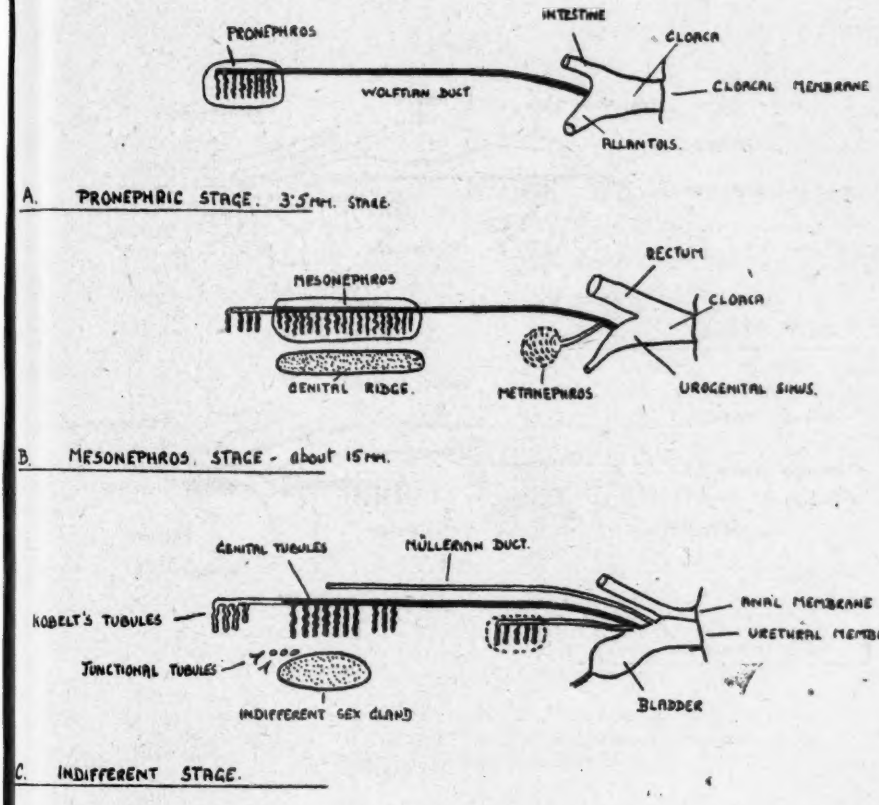


FIG. 1.

Diagrams showing the development of the female and the male urogenital apparatus. (Adapted from Gideon S. Dodds.)

B.G.

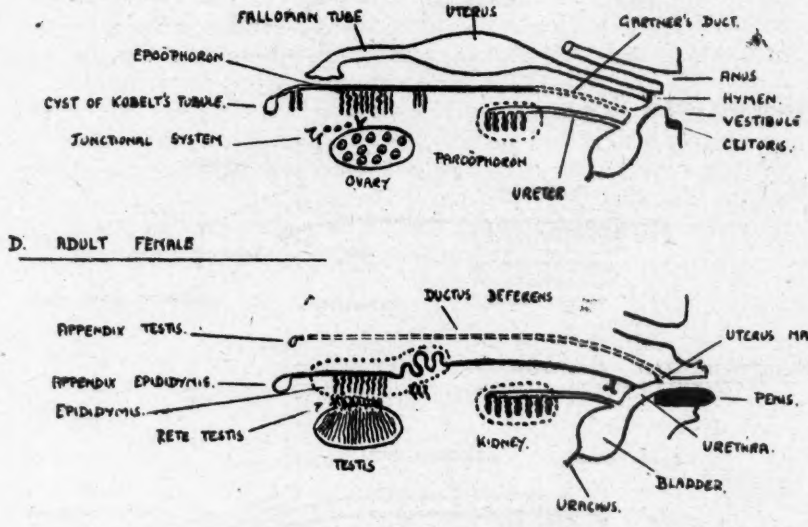


FIG. 1 (*continued*).

Diagrams showing the development of the female and the male urogenital apparatus. (Adapted from Gideon S. Dodds.)

B.G.

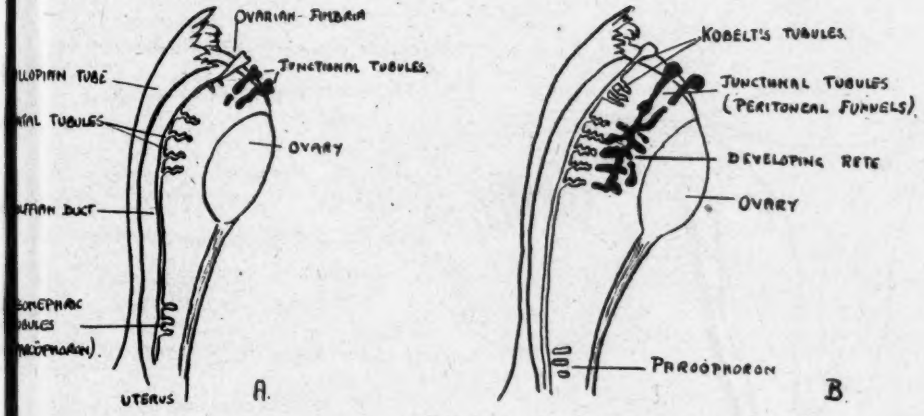


FIG. 2.

A. The Müllerian duct, Wolffian duct, ovary and the beginning of the junctional system. From the margin of the broad ligament over which the ovarian fimbria runs, solid cords of cells, representing peritoneal funnels, are formed and grow into the Wolffian mesentery: these are the rete or junctional cords.

B. The junctional cords have grown and send branches to unite with the Wolffian genital tubules, and in the case of the male with the seminal tubules. In the female such tubules do not exist and the rete or junctional tubules remain either as solid cords or as tubular structures near the hilum of the ovary or even in the substance of the ovary. (After Allen & Keith.)

B.G.

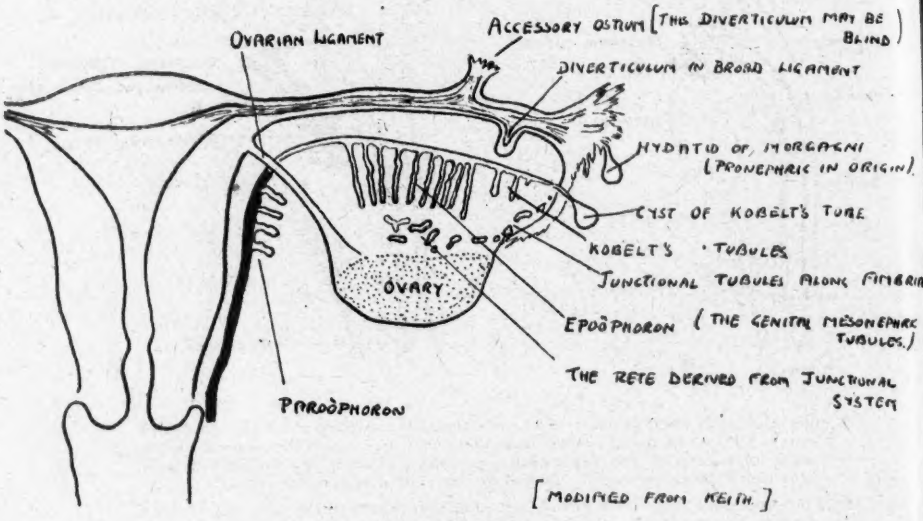


FIG. 3.

Diagram showing the residual urogenital structures which are present in the broad ligament. Cysts may arise from any of these structures. Shaded portion of the Wolffian duct normally disappears; when present it is known as Gartner's duct.

B.G.

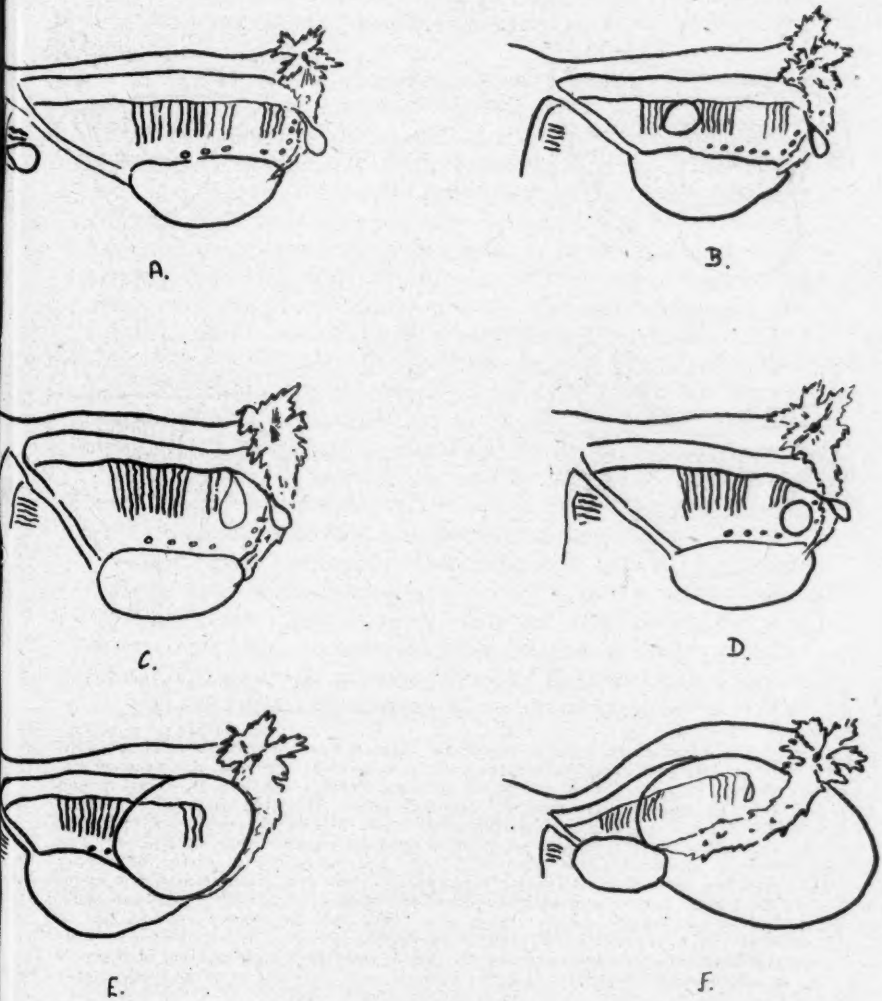


FIG. 4.

B.G.

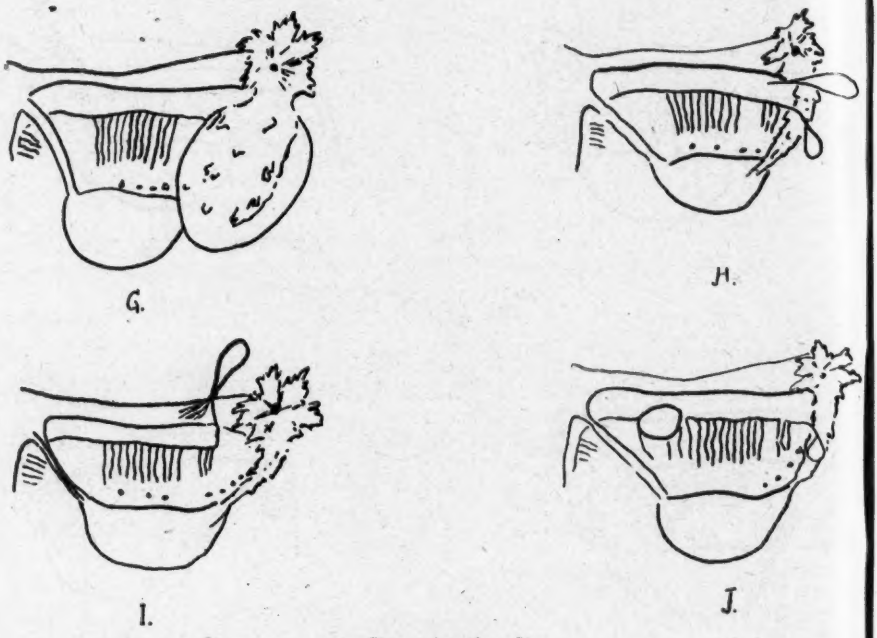


FIG. 4 (*continued*).

THE VARIOUS TYPES OF CYST ARISING FROM THE VESTIGIAL STRUCTURES IN THE BROAD LIGAMENT (EXCLUDING GARTNER'S DUCT).

(A) A cyst arising in the paroöphoron: these cysts are usually small. The remains of the rete runs along the ovarian fimbria, and in the region of the hilum of the ovary. There is a small cyst of the terminal Kobelt's tubule. (B) A cyst arising from the epoöphoron: these are generally small. (C) Cysts of Kobelt's tubules. (D) A small cyst arising from the vestigial rete (junctional system). (E) The rete or junctional cyst is larger: the Wolffian relics are separate from the cyst. (F) The rete or junctional tubule cyst is still larger and the tube and ovarian fimbria are stretched out over it. (G) A rete or junctional tubule cyst arising immediately under the ovarian fimbria which is thinned and spread out over it. (H) A small cyst probably of pronephric origin. Some have called this an accessory hydrosalpin of Müllerian origin. (I) A cyst, probably pronephric in origin. It is connected with the Fallopian tube and may represent (A. Keith) the former close relation of the pronephros and the Wolffian and Müllerian ducts. (J) The rare cyst of the Wolffian duct proper: they are usually small.

B.G.

the rete testis in the male are different. The rete testis consists of a series of anastomosing tubes which are merely channels in a fibrous stroma, lined by flattened epithelium and not having any proper walls. The thin membrane by which they are lined bears a striking resemblance to the peritoneum from which they are derived.

If we now take a transverse section across the outer end of the Fallopian tube and broad ligament down to the level of the ovary the microscope reveals that enclosed in the connective tissue two distinct tubular sets are to be seen. First, a set of tubules provided with thick muscular walls lined for the greater part with columnar cells which are generally devoid of cilia, but a few may be seen in some specimens. Secondly, a set of tubules with extremely thin walls and not provided with a coat of muscle. Of these two groups the first represents the genital mesonephric tubules and the second group represents the junctional tubules. The junctional tubules arising in the manner already described are also found along the length of the ovarian fimbria. At this point it should be noticed that ovarian substance is often prolonged in a tail-like manner along the fimbria (representing part of the old diaphragmatic fold), and in this way some of the tubules may become incorporated in the substance of the ovary. These are of importance in the histogenesis of certain ovarian tumours.

The original mesonephric tubules persist between the uterus and the ovary: these tubules, the tubules of the paroöphoron, represent those which originally behaved as excretory ducts of the mesonephros. In both the male and female they persist as minute elements and indicate a greater degree of retrogression than do the genital tubules which are of great functional importance in the male.

## Theoretical Varieties of Cyst which may be found in the Broad Ligament

1. *Cysts Derived from Müllerian Elements.*

In the course of development cells of Müllerian type or of similar origin may become separated from their fellows and come to lie in the substance of the broad ligament. Now, we know that Müllerian tissue in its upper part gives origin to the ciliated columnar and secretory columnar epithelial cells of the Fallopian tube, the tubular glands of the corpus uteri and the compound racemose mucous glands of the cervix.

It follows that cysts lined by tube-like, endometrium-like and cervix-like epithelium may be found in the broad ligament. The former give origin to serous cysts lined by ciliated columnar epithelium (the cilia may disappear in large cysts and in cysts which occur in old patients): the second group to endometriomata (more commonly found in the ovary than in the broad ligament), and the third, to the pseudomucinous cystoma. These may occur anywhere in the broad ligament as the Müllerian duct traverses this structure from end to end.

(For further observations on cysts derived from the fully formed Fallopian tube see the discussion.)

2. *Cysts Derived from Pronephric Elements.*

It has been shown that there is reason to believe that the hydatid of Morgagni is of pronephric origin, and it is also probable that the little cystic process often seen running from the distal end of the Wolffian duct is of the same origin. Sometimes 2 or 3 pedunculated cysts instead of 1 may be found at this point: when present these are called Kobelt's cysts. In some cases a connective tissue junction may exist between the distal end of the Wolffian duct and the end of the Fallopian tube; a small cyst which is presumed to be of pronephric origin may occasionally be found in this. A specimen of this nature is to be seen in the museum of the Royal College of Surgeons, London.

Pathological cysts derived from these structures are always small and lined by flattened epithelium.

3. *Cysts Derived from the Wolffian Elements.*

Theoretically a cyst may arise from the residuary duct, from the genital tubules (representing the epididymis of the male), and from the residuary nephric tubules (the paroöphoron).

Cysts of the horizontal part of the Wolffian duct are very rare, but cysts of the lower part, Gartner's duct, which is generally absent in women, are rather more common.

The vertical genital tubules sometimes undergo cystic change. The cyst is small and is lined by columnar epithelium usually devoid of cilia, but they may be present, and it is surrounded by a coat of unstriped muscle fibres.

Cysts may also form in the residuary nephric tubules. These too are small and are placed near the uterus. Such cysts are lined by columnar or sub-columnar epithelium.

4. *Cysts Derived from the Junctional Tubules.*

These will arise along the area representing the diaphragmatic fold along which the ovarian fimbria runs in the fully developed apparatus and in the hilum of the ovary, since this is the area where they develop to form the rete testis. Cysts derived from the junctional tubules may reach large dimensions; this is the common cystic tumour of the broad ligament. By virtue of their anatomical position these cysts cause the fimbriated portion of the Fallopian tube to stretch out over them and the ovarian fimbria is naturally much stretched and thinned. These junctional cysts are sometimes called fimbrial cysts, but it will be realized that this name is incorrect because the cyst does not spring from the normal structure of the fimbria.

Junctional cysts are lined by a single layer of extremely thin epithelium (it will be remembered that they are derived from minute peritoneal funnels) and their supporting wall is the connective tissue of the broad ligament, which is compressed by their growth to form a fine capsule. Muscle fibres are not present as they are in the walls of cysts derived from the genital tubules.

## The Relation of Cysts of the Broad Ligament to Torsion

It will be appreciated that torsion of cysts of the broad ligament is a rare phenomenon since the cyst is effectively retained in position by the anterior and posterior peritoneal layers of the ligament. Torsion would appear to be possible under two conditions: (1) when the cyst is so enormous that the original structure of the broad ligament is, by comparison, converted into a thin pedicle; and (2) when the cyst originates in the area outlined by the ovarian fimbria, the ovary and the adjacent part of the Fallopian tube. A cyst in the second position is relatively free and it is possible for a movement of rotation to be executed with the uterine cornu as the point about which rotation takes place. The number of turns will be limited by the available length of the broad ligament peritoneum which becomes elongated and laxer than usual when cysts occur in this position. The Fallopian tube and ovary will naturally undergo torsion with the cyst.

The following is a clinical and pathological account of such a cyst which had undergone torsion.

*Case Record.*

The patient was a woman of 76 years who was admitted to

hospital on August 8th, 1940, with a history of abdominal pain and vomiting.

She had noticed a swelling in the left iliac and lower lumbar region for some years. Six weeks previously she had had an attack of severe abdominal pain and vomiting which was, however, relieved by rest. During the week prior to her admission to hospital she had 3 similar attacks, the last one being accompanied by repeated vomiting. The bowels had not been open for the last 3 days: an enema ordered by her general practitioner had yielded a good result but did not relieve her symptoms.

Examination revealed distension of the lower half of the abdomen, visible peristalsis, and borborygmi were heard. A hard, fixed tender mass was palpable in the left ilio-lumbar region. On rectal examination a hard mass was felt in the pouch of Douglas.

Laparotomy revealed the presence of free blood-stained fluid in the peritoneal cavity. The caecum and transverse colon were moderately distended and the left side of the lower abdominal cavity and pelvis were filled with a large tense reddish-purple mass. Digital exploration showed that this mass consisted of a cyst which had undergone torsion, the axis of rotation being at the line of junction of the Fallopian tube with the uterus. On untwisting the pedicle a grossly distended purple Fallopian tube became visible in its whole length. The ovary, which was also large and purple in colour, was separated from the Fallopian tube by a cyst of approximately 4 inches diameter. The uterus was the seat of a large partially calcified fibroid. The uterus with the tumour could not be lifted out of the pelvis.

The Fallopian tube, the ovary, the cyst and neighbouring structures of the broad ligament were removed in one piece. At this stage the patient's condition did not justify further attempts at mobilizing the uterus; a flatus tube was passed up to the level of the distended pelvic colon and left *in situ*.

In view of the patient's condition it was considered wise to close the abdomen as soon as possible. The fibroid was left and the abdomen closed after the usual peritoneal toilet. The patient was discharged on August 26th, having made an uneventful recovery.

*Microscopic examination.*

Several portions of the specimen were submitted to microscopical examination.

(*a*) *The Cyst Wall.*

This was sectioned in two places each of which was found to present the same histological picture.

The epithelial wall is composed of a single layer of cells which consist chiefly of nucleus, the cytoplasm being in such small quantity that it is difficult to see. Here and there microscopic papillae are to be seen; each is covered with epithelium of the same type, the base is wide and the core is composed of coarse connective tissue. Nowhere in the sections examined are cilia to be seen. The epithelium rests on connective tissue elements between which many red blood cells are to be seen. The vessels are thrombosed. The colloid material of the cyst stains uniformly blue.

(*b*) *Section of the Ovarian Fimbria and Cyst Wall.*

The section is taken at that point where the ovarian fimbria runs across the wall of the cyst. The fimbria is oedematous and the spaces between the connective tissue fibres are filled with blood-cells. The vessels are thrombosed. The most remarkable feature of the fimbria is that they have lost their epithelial covering, presumably as the result of torsion. The cyst wall which lies immediately below the fimbria presents the features already described.

(*c*) *The Fallopian Tube.*

The tube has been sectioned at its uterine extremity; the section shows tubal epithelium characteristic of the interstitial portion, i.e. devoid of plicae. The tissue in immediate relation to the epithelium is infiltrated with blood. Outside this is a layer of circular muscle which is remarkable for its normal appearance and lack of interstitial haemorrhage. Outside this again is the muscle of the uterine wall into which diffuse haemorrhage has taken place. Torsion, therefore, occurred through the uterine cornu.

In the broad ligament below the Fallopian tube there is a structure cut transversely, which is lined by a single layer of epithelium exactly like that lining the cyst. It contains some colloid secretion which stains in a manner similar to the secretion inside the cyst.

The cyst has, therefore, been derived from a structure of this nature which is recognized as representing the remains of a junctional tubule.

The important observations are:

(1) The thin epithelium composed of a solitary layer of cells.
(2) The absence of cilia.
(3) The epithelium is the same as that lining the remnants of the rete ovarii.
(4) The absence of unstriated muscle in the cyst wall.

## Discussion

It will be granted that any cyst which occupies the space between the two peritoneal layers of the broad ligament is worthy of the general name of broad ligament cyst. One commonly finds the term "parovarian cyst" used to indicate the fairly common, large, thin-walled cyst of the broad ligament. Since Bantock's work on this subject, published in 1873, it has been believed by gynaecologists that all cysts developing between the layers of the ligament, whether above or below the Fallopian tube, are of parovarian origin.

Before proceeding further with this discussion it is important to mention what the accepted textbooks mean when they refer to parovarian cysts. "Ten Teachers'" textbook on gynaecology states that the term parovarium includes the following structures: (1) Gartner's duct, (2) Kobelt's tubules, (3) the epoöphoron, and (4) the paroöphoron, and any cysts arising from these structures are referred to by the authors as parovarian cysts. The junctional tubules are neglected in the usual definitions.

We have shown above that Gartner's duct does not normally exist in the human female. The duct was originally described by Gartner in certain animal species, and is the accepted name for that part of the Wolffian duct which traverses the wall of the uterus and the vaginal wall. The upper part of the Wolffian duct is, therefore, wrongly called by Gartner's name.

In addition there are certain other views which are of importance in any discussion on the histogenesis of cysts in this situation. Kossmann[3] maintained that broad ligament cysts in general are of Müllerian origin, but little evidence has been accumulated in support of this view.

Starting from first principles it is clear that cysts may arise from the following structures:

(1) The hydatid of Morgagni (attached to the ovarian fimbria).

(2) Kobelt's tubules, the terminal ones may be pedunculated.

(3) The tubules of the epoöphoron (the genital mesonephric tubules).

(4) The Wolffian duct in the broad ligament.

(5) The tubules of the paroöphoron.

(6) The junctional tubules.

(7) From diverticula of and accessory Fallopian tubes.

(8) From Gartner's duct in the uterine wall (these usually point in the vaginal fornix).

(9) From cells of high potential which take origin from the nephrogenic cord and become incorporated in the substance of the broad ligament: as a result of an unknown stimulus they develop into cysts which are found in the broad ligament or in the ovary. Mesonephromata come in this group.

(10) From connective tissue structures, e.g. canalized endotheliomata.

These sites of origin may be looked upon as falling into two classes, namely, cysts derived from primitive cells of high potential, which are rare, and cysts derived from the vestigial structures, which are common.

Most of the cysts which one meets in practice are large and have very thin walls. Sometimes these cysts grow to considerable size such as the one recorded by Irvine[16] which he removed after performing two paracenteses: this cyst weighed 100 pounds. Hutchinson[24] has recorded another one which he removed from a woman who had had 11 confinements at full time, 4 of these having occurred since the tumour was first detected. This cyst was first tapped and 31,000 c.c. of fluid were withdrawn and after enucleation a further 5,000 c.c. were obtained. This volume corresponds to about 9½ gallons.

It is possible to demonstrate every stage in the development of these cysts from minute ones in the direct vicinity of the fimbria to enormous broad ligament cysts. These cysts are derived from the junctional system. When they are of relatively small size they are generally known to gynaecologists as fimbrial cysts. This is unfortunate, because the cysts are not primarily of fimbrial origin, and if and when we encounter a true cyst derived from fimbrial tissues we shall be unable to employ the expression "fimbrial cyst" since it is already erroneously employed to describe the common form of cyst in this part.

Cole[7] dealt with most aspects of these vestigial structures in the broad ligament in a masterly article written some 30 years ago. He has dealt thoroughly with the histology of the vestigial

structures which are normally present in the broad ligament, with the exception of the junctional system.

Prior to 1910 it was the general opinion that cysts in the broad ligament originated from the parovarium. Kossmann, however, held the view that they originated from accessory Fallopian tubes: this view has been destructively criticized by Meyer.

Nevertheless, in connexion with the possible Müllerian origin of certain cysts we recall the work of Sampson Handley[5] in 1903, in which he contended that cysts which could be enucleated and which were situated above the Fallopian tube were of Müllerian origin. He was able to substantiate this view by demonstrating a communication between a Fallopian tube and a cyst lying above it (R.C.S. Museum, Spec. No. 4582). He furnished additional evidence by demonstrating the similarity of a hydrosalpinx to the cyst wall.

It would appear that cysts of this nature may form from tubal diverticula which, obviously, may be either intra-peritoneal or intra-ligamentous. The types described in the literature seem to be of the intra-peritoneal variety and hence the cyst would lie above the Fallopian tube. If, on the other hand, an intra-ligamentous diverticulum were similarly affected we should then have a broad ligament cyst of Müllerian origin, in this case taking its origin from the adult Fallopian tube and not from certain embryonic rests which have remained in the tissues for years before undergoing further development. A cyst derived in this way would lie below the Fallopian tube differing from the specimen described by Sampson Handley: Müllerian cysts may, therefore, lie above or below the Fallopian tube, but most of the cysts of this variety which have been found lie superior to the Fallopian tube.

The properties of cysts arising from the individual parts of the vestigial structures have been described higher up, and it will, therefore, be clear that on macroscopic examination in the operating theatre it is not easy to determine the exact structure from which a cyst arises. Nevertheless, one can say that the large broad ligament cysts, such as pictured in the textbooks on gynaecology, are derived from the junctional tubules, whereas small cysts, such as those shown in Fig. 4, are derived from those vestigial structures which may be called the parovarium, i.e. the Wolffian duct in the broad ligament and the genital and nephric tubules.

It should be possible for the pathologist, given sufficient tissue,

to say whether any particular cyst is a junctional tubule (rete) cyst or whether it is derived from any of the diverticula of the vestigial Wolffian duct.

It will be appreciated that the loose use of the term "parovarian cyst" is to be deprecated, particularly in view of the fact that so many of the cysts which form in the broad ligament are not of parovarian origin according to the accepted definitions of the parovarium. It would, in fact, be best to drop the use of the expression "parovarian cyst" and substitute the non-committal simple one "broad ligament cyst", thus leaving the determination of the site of origin to the pathologist.

Before leaving this subject let us consider the other varieties of cyst which may be found from time to time in this area. Some of them can be proved to be of ovarian origin by finding their direct attachment to the ovary. In other cases the association is not so clear; in this connexion we would like to draw attention to a patient who recently came under our care in whom an enormous cyst of the multilocular pseudomucinous variety, which extended retro-peritoneally into the retro-cervical and retro-vaginal tissues, had no demonstrable ovarian connexion, the ovaries of each side being absolutely normal and not exhibiting any attachment whatever to the cyst. Histologically this cyst had exactly the same characteristics as the multilocular pseudomucinous cystoma of the ovary. It must, therefore, have been derived from some residual elements trapped in the connective tissue of the broad ligament and have subsequently developed into a cyst. It is clear that the origin of a cyst of this kind has certain points in common with the histogenesis of ovarian tumours proper. The only reasonable explanation of the origin of such cysts is that they are derived from embryological rests.

Now, cysts arising in the middle of the broad ligament will not be likely to undergo rotation since they are bound down by the anterior and posterior layers of peritoneum. On the other hand, cysts arising from the original cephalic end of the genital ridge, thereby coming to lie between the region of the abdominal ostium of the Fallopian tube and the ovary, i.e. along the ovarian fimbria when full development is attained, are in a relatively mobile position.

Any enlargement of the vestigial junctional tubules will result in the area becoming mechanically unstable, with a tendency for the Fallopian tube to rotate about its junction with the body of the uterus. In other words, if a cyst of the broad ligament

undergoes torsion it will be one which is primarily placed in the angle formed by the ovarian fimbria and the ovary: in nearly all cases it will be of junctional origin. Most of these cysts have a smooth lining, but when they have been present for some length of time they may exhibit coarse flat papillae.

It also follows that if any elements of junctional epithelium should, in the course of development, be included in the hilum of the ovary or in the ovarian substance they may give origin to cysts which will be considered to be primarily ovarian. Their histology will naturally be the same as that already described for junctional cysts in their normal habitat.

These observations on the junctional system may be applied still further, viz. in connexion with the inclusions which were first described by Werth in 1887, but which were fully described by Walthard in 1903 and subsequently re-studied by Akagi in 1928. These so-called Walthard cell islands are generally to be found in the superficial portions of the ovary, but they may also be discovered deeper in the ovarian substance. Their distribution, however, is not limited to the ovary, since they are often seen in the Fallopian tube and also in the ligaments attached to the uterine cornua; their distribution suggests that at some time in their developmental history they took origin from the peritoneum in the region of the ovary in a manner similar to that already described for the junctional tubules.

The Walthard islands have attracted considerable attention during recent years since they have been shown to undergo central liquefaction which may progress to actual cyst formation. Some pathologists maintain that the Walthard islands give origin to the Brenner tumour, concerning which there are several theories of origin which are outside the scope of this paper.

The significance of peritoneal funnel formation, which in the human results in the production of solid columns of cells, the cross-section of which resembles a Walthard island, will not fail to be recognized in the histogenesis of the Brenner tumour. This theory of origin differs on academic grounds from those which are recorded in gynaecological textbooks.

## Summary

(1) The origin of the vestigial structures of the broad ligament and mesovarium are described, including the origin of the pronephros, mesonephros, metanephros and the gonads.

(2) The junctional tubular system is considered in detail with its pathological significance.

(3) The fate of the pronephric, Wolffian and Müllerian systems is considered.

(4) The sites of origin of broad ligament cysts are deduced from the embryology and the special features of each variety of cyst are described.

(5) The clinical history and pathology of a broad ligament cyst which had undergone torsion is given.

(6) In the general discussion the special features of junctional tubule cysts are presented, together with the mechanism of torsion.

(7) The loose use of the term "parovarian cyst" is criticized and other recommendations made.

(8) Suggestions are made concerning the origin of the Walthard islands and Brenner tumours.

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# Puerperal Infection associated with Haemolytic Streptococci other than Lancefield's Group A

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IT is generally accepted that the majority of human streptococcal infections, including puerperal infections, are caused by haemolytic streptococci belonging to Lancefield's group A. Eden and Holland[1] considered group A haemolytic streptococci "the only ones capable of causing severe invasive infections in the human species." In the 1939 edition of "Queen Charlotte's Textbook of Obstetrics," it is stated that "streptococci belonging to group A are practically the only ones capable of causing severe invasive infections in human beings". However, haemolytic streptococci belonging to groups other than A have been isolated from the genital tract both apart from and associated with puerperal pyrexia. Lancefield and Hare[2] isolated 66 strains of haemolytic streptococci from 65 puerperal women who were either uninfected or had only a slight increase of temperature during the puerperium. Of these only one strain was group A; the remaining were as follows:—group B 26; group D 26; group C 5; group G 3; group F 2, and 3 unclassified strains. In 18 cases with "minor infections" the distribution of isolated streptococci was:—group D 8; group B 7; group C 1; group G 1; unclassified 1. There was doubt in most of these cases whether the pyrexia was really due to a uterine infection. In contrast, the strains from 46 cases of streptococcal puerperal infection of the uterus belonged, with one exception, to group A. They, therefore,

concluded that group A haemolytic streptococci were responsible for all severe cases of infection and that "the vast majority of haemolytic streptococci from the birth canal which do not bring about active infections are not members of this group. Most of them fall into either group B or D".*

In 1930, before the advent of Lancefield grouping, Taylor and Wright[3] had analysed the vaginal flora of 1123 women before delivery. From 32 (2.85 per cent) true haemolytic streptococci were isolated—from their description a number of these were almost certainly group B—and in 22 (1.96 per cent) pseudo-haemolytic streptococci, presumably group D, were found; that is to say 4.8 per cent of their cases showed haemolytic streptococci in the vaginal flora before delivery. They could not discover any evidence that these organisms gave rise to infection in the puerperium.

In contrast to these findings, several authors in recent years have reported cases of severe and fatal puerperal infections in which the causative haemolytic streptococci belonged to groups other than A. Fry[4] described 3 fatal post-partum group B infections, 2 being associated with endocarditis. Colebrook and Purdie[5] reported a case of acute endocarditis due to group B streptococcus; death from cerebral infarct occurred after 4 days' treatment. They also recorded 2 patients from whose blood group G haemolytic streptococci were recovered but had probably no aetiological relation to the infection. Macdonald[6] reported 3 cases of group G streptococcus infection in 2 of which the patients had died from infective endocarditis; neither of these infections was puerperal. The third patient who recovered had a post-abortum puerperal infection which was moderately severe. Lately, Hill and Butler[7] in an analysis of 110 consecutive cases of haemolytic streptococcal infection occurring in Melbourne found that 28 were due to infections with haemolytic streptococci of groups

* The probable explanation for the preponderance of strains belonging to groups B and D among haemolytic streptococci present in the genital tract of healthy women antepartum is that organisms of these two groups are strongly resistant to acid and, therefore, withstand the high acidity of the normal vaginal secretions. *Streptococcus pyogenes* (group A) cannot survive in the healthy vagina and the same probably applies to groups C and G strains which *in vitro* do not produce a high degree of acidity in glucose-broth. Thus streptococci of groups A, C and G are mostly introduced into the genital tract from an outside source, and their presence there would *a priori* be more suggestive of an infection due to them than would be the case with strains belonging to groups B and D.

other than A. Of these, 12 were group B, 10 group C and 6 group G; 4 of the group B cases proved fatal, 3 of them being post-abortum. They indicated strong points of resemblance to Fry's fatal cases, both as regards the clinical course and in the post-mortem findings of acute infective endocarditis in 2 cases. The groups C and G cases were for the most part mild, but one case of fatal group C infection not in their series had occurred at an earlier date in the same hospital.

## Present Investigation

It was the occurrence of 3 fatal cases of streptococcal endocarditis, 2 group B and 1 group G, in the Puerperal Sepsis Unit at the North-Western Hospital during the past year which led us to analyse our records of cases associated with haemolytic streptococci other than group A during the 4 years 1937-40. The histories of the 3 fatal cases will be first described, followed by an analysis of the cases from which haemolytic streptococci belonging to groups B, C, D, G and unclassified were isolated.

Case 1.

Aged 36, multipara 1. The patient had always been in good health; there was nothing to suggest any pre-existing cardiac disease. On April 11th, 1940, she had a spontaneous abortion at 8 weeks. Ten days later she was admitted to a L.C.C. general hospital with a diagnosis of broncho-pneumonia, and a history of fever for the previous 3 days. There was no evidence of any gross sepsis of the genital tract or of pelvic inflammation; haemolytic streptococci were not found in the vaginal swabs; urine and blood cultures were negative. She was treated with M. & B. 693, having 6 grams daily from April 21st to April 27th, and 3 grams daily from April 27th to April 29th without obvious effect; the temperature continued to swing between 101°F. and 104°F. and the drug was stopped on account of leucopenia and a morbilliform rash. Pyrexia persisted and on May 9th a blood culture gave a growth of haemolytic streptococci, when the patient was transferred to the North-Western Unit. On admission her general condition was good. There were signs of thickened pleura over the right lung, but no clinical evidence of sepsis of the genital tract. The first sound at the apex was thumping and hard; the pulse-rate varied between 112 and 140. A remittent pyrexia persisted throughout the course of the disease until 2 days before death when it dropped to normal; the pulse-rate remained high throughout. The patient never complained of pain or discomfort but became increasingly drowsy and stuporose. Death occurred on May 29th after an illness which had lasted 48 days. Culture from the cervix on May 10th showed one colony of haemolytic streptococcus. The urine was sterile. Haemolytic streptococci belonging to Lancefield's group B were grown from blood culture on five occasions, the counts being: on May 10th, 65 organisms per c.c.; May 14th, 7; May 22nd, 18; May 25th, 138, and

May 29th, 14 organisms per c.c. As M. & B. 693 had already been administered without benefit, sulphanilamide was given in doses of 9 grams daily from May 18th to May 24th. Then M. & B. 760 (sulphathiazole) was given in large doses commencing with 15 grams in the first 30 hours and thereafter at the rate of 6 grams daily. The disease was by now too far advanced to constitute a fair test of the drug.

The report on the autopsy (coroner's post-mortem) was as follows: The uterus was slightly enlarged and contained fragments of material consistent with retained products of conception. Signs of obvious sepsis and of mechanical injury were absent. The heart was normal in size but the muscle was somewhat flabby. There was a large solid vegetation on the mitral valve. The lungs were congested and oedematous. The liver was fatty; the spleen was enlarged and soft and there was one fairly recent liquefying infarct. The kidneys showed cloudy swelling and the left one had a small recent infarct. The adrenals, bladder, stomach, intestines, brain and central nervous system were normal.

CASE 2.

Aged 26, primipara. After a normal pregnancy the patient was admitted to a L.C.C. general hospital on September 11th, 1940, with severe antepartum haemorrhage; she was then 3 days short of full-time. A marginal placenta praevia was diagnosed and Willett's forceps applied; on September 12th a still-born child was delivered normally after a labour which had lasted 25 hours. Pyrexia commenced on September 14th. Cervical and blood cultures were then negative; pus cells and albumin were present in the urine and staphylococcus aureus grew on culture. On September 22nd an abscess of the buttock was incised; staphylococcus aureus was grown from the culture. Cultures from nose, throat, cervix, urine and blood were still negative. On October 4th a small pleural effusion developed at the left base. On October 14th a haemolytic streptococcus was grown on blood culture and on October 17th the patient was transferred to this unit. During her stay in the general hospital she had been treated with sulphanilamide, 84 grams in all being given in the first 14 days; this was followed by 9 grams of sulphathiazole (M. & B. 760) but, as no response had been obtained, sulphonamide therapy was discontinued and two blood transfusions, each of 1 pint, were given on October 14th and October 16th.

On admission to the unit the patient was not unduly ill or toxic. There was no evidence of any sepsis of the genital tract and the uterus was small and involuted. A diastolic bruit was heard at both apex and base. The temperature fluctuated between 100°F. and 104°F. during the first 4 days in hospital. Sulphapyridine was given and the temperature practically settled to normal but commenced to swing again after November 1st, and throughout the remainder of the course there was a marked undulation of pyrexia, periods of remittent or intermittent temperature being followed by almost complete subsidence of fever.

A haemolytic streptococcus belonging to Lancefield's group B was isolated by blood culture on 7 occasions; the counts were as follows: October 18th,

6 organisms per c.c.; October 24th, less than 1; November 5th, 17; November 10th, 3; November 14th, 5; November 19th, 2, and November 30th, 2 organisms per c.c. Blood cultures were sterile on 4 occasions (October 31st, November 15th, November 29th, and December 4th). Staphylococcus aureus was isolated from the nose, throat, cervix and urine on admission; haemolytic streptococci were not isolated from any of these sources. B. coli and pus cells were frequently found in the urine during the course of the illness.

Sulphonamide therapy was given as follows:

Sulphapyridine: 37 grams between October 19th and 29th.

Sulphanilamide: 47 grams between November 6th and 15th.

Sulphapyridine: 29 grams between November 26th and December 4th.

The absorption of the drug was fair, the estimations in the blood being as follows: October 21st, free sulphapyridine 6.0 mgm. per 100 c.c.; November 8th, free sulphapyridine 5.0 mgm. per 100 c.c., and December 4th, free sulphapyridine 11.0 mgm. per 100 c.c.

An autogenous vaccine was prepared and given at 4-day intervals in gradually increasing dosage between November 5th and December 10th; it commenced at a dose of 10 million organisms and increased to 100 million. Blood transfusions of 1000 c.c. were given on November 12th and November 16th. On November 16th, the pyrexia had again settled to normal and the general condition was improved. The temperature, however, soon began to rise once more and the patient's condition deteriorated. Immunotherapy with blood taken from the husband, who had been given a course of the vaccine, was commenced on November 27th and repeated on December 5th, December 16th, December 23rd, and December 30th, 400 c.c. being given on each occasion. There was now little response to treatment, and death ensued on January 4th, 1941, after an illness which had lasted 111 days. The post-mortem report (by M. G.) was as follows:

*External appearances*: well-developed, emaciated woman.

*Larynx, pharynx, trachea and oesophagus*: clear.

*Heart*: pericardium slightly distended with clear yellow fluid. Heart not enlarged, milk spot at apex of right ventricle. Cavities contained some ante-mortem clot. Aortic, tricuspid and pulmonic valves healthy. Mitral valve almost completely occluded by fairly massive crumbling vegetations which protruded upwards into right auricle. Muscle soft, not markedly hypertrophied.

*Lungs*: free, bases markedly oedematous and congested, pus in bronchioles, no obvious broncho-pneumonia.

*Abdomen*: omentum strongly adherent to undersurface of floating ribs on left side, no obvious peritonitis. A large mass about 5 cm. in diameter was present in the mesentery of the small intestine lying between right kidney and lumbar vertebrae. The mass was found to be laminated blood-clot. The intestines were generally slightly congested but otherwise unaffected by the mesenteric thrombosis. The stomach contained bile-stained fluid.

*Liver*: slightly enlarged, congested.

*Spleen*: about twice normal size, substance congested with soft numerous

triangular areas of yellow necrotic material, largest about 2 cm. in depth on surface (septic infarcts).

*Kidneys, Left*: enlarged, congested, necrotic septic infarct about 2 × 1 cm. at upper pole. *Right*: enlarged, congested. Numerous septic infarcts, largest about 3 cm. in central portion of kidney.

*Uterus*: well involuted, endometrium congested. No obvious sepsis. *Cervix*: slightly lacerated, small amount of purulent exudate present. Left iliac vein contained firm clot.

*Brain*: congested and oedematous, small abscess just below convolutions in upper part of right parietal lobe.

*Other organs*: no marked abnormality.

CASE 3.

Aged 30, multipara 4. A self-induced abortion of a 12-weeks pregnancy occurred on May 1st, 1940. On May 3rd the patient was admitted to a L.C.C. general hospital and foul retained products were removed under general anaesthesia. Pyrexia commenced on May 4th, and fluctuated between 99°F. and 101°F. until May 9th when it commenced a steeper swing of 99°F. to 104°F. A vaginal swab showed anaerobic streptococci together with staphylococcus albus and diphtheroids. Haemolytic streptococci were not isolated until May 10th, when they were obtained on blood culture. The patient was given M. & B. 693 in doses of 3 grams daily from May 3rd to May 8th, and 6 grams daily from May 8th to May 10th. As the temperature was still rising, she was then given sulphanilamide 6 grams daily until May 12th when she was transferred to this unit. On admission she was extremely toxic and ill; the skin was hot and dry and the tongue heavily coated. The uterus was bulky and tender, but there was no evidence of either pelvic or general peritonitis. The temperature continued to swing between 98°F. and 103°F. or 104°F. for the first 7 days and then became more mildly remittent, rising to a continuous level of 101°F. to 103°F. before death. On May 17th the patient had two severe rigors; these recurred on May 21st and it was then noticed that she had difficulty in speaking and there was a loss of power in the right hand but not in the right leg. She died on June 9th, after an illness lasting 36 days.

Blood cultures were carried out on 4 occasions and haemolytic streptococci of Lancefield's group G were grown; the counts were as follows: May 13th, 250 organisms per c.c.; May 15th, 360; May 20th, 125, and May 21st, 105 organisms per c.c. The organism was also grown from the cervical culture on May 13th.

From May 12th to May 15th, sulphanilamide was given in doses of 6 grams daily. On May 15th, M. & B. 693 was given 2 grams intravenously and 6 grams intramuscularly. Each intramuscular injection became rapidly septic and there was considerable vomiting, so prontosil album was given from May 17th to May 24th in doses of 9 grams daily. From May 24th, M. & B. 760 (sulphathiazole) was given 15 grams in the first 30 hours and then at the rate of 6 grams daily. The sulphonamide drugs were poorly absorbed as the following figures of blood-concentration show: on May 15th free sulphanila-

mide = 0.75 mgm. per 100 c.c., total sulphanilamide = 1.25 mgm. per 100 c.c.; on May 20th free sulphanilamide = 3.5 mgm. per 100 c.c., total sulphanilamide = 6.0 mgm. per 100 c.c.; on May 31st free sulphathiazole = 1 mgm. per 100 c.c. During this time the patient's condition was becoming steadily worse and from June 3rd to June 7th sulphanilamide was again given in doses of 9 grams daily. She was then rapidly sinking and therapy was discontinued.

The report on the autopsy (coroner's post-mortem) was as follows: Uterus slightly larger and softer than normal; cervix dilated, softer than normal; no evidence of sepsis; no mechanical injury. Heart muscle rather soft and fatty; chronic thickening of mitral cusps and many large recent crumbling vegetations; one minute recent vegetation of the aortic cusp. Lungs, marked congestion and oedema. Liver extremely fatty; spleen enlarged, soft and toxic, containing several recent infarcts; kidneys pale and cloudy with small haemorrhages. The adrenals, bladder, stomach and intestines were normal. The brain showed a large area of softening on the left side starting in the temporal lobe and spreading upwards and backwards.

In the clinical analysis of the remaining cases, it was essential to determine whether sepsis of the genital tract was present, and if so, whether the sepsis was due to the associated streptococcus. Pyrexia associated with bulkiness or persistent subinvolution of the uterus, or the presence of offensive or purulent lochia constituted the main criteria of a genital tract infection. When there was any doubt about the aetiology of the pyrexia, *e.g.* if other pathogens to which the infection might be attributed were present or there was evidence of extragenital infection, the cause has not been attributed to the haemolytic streptococcus. In this way we tried to determine, as fairly as possible, whether the streptococcus isolated from the genital tract was responsible for the puerperal infection or was merely an accidental finding. Blood culture, nose and throat cultures, and a complete haematological examination were made in most of the cases. Two patients in whom the haemolytic streptococcus was recovered from the blood but not from the genital tract are included; cases in which haemolytic streptococci, usually group D, were found only in the urine have been excluded.

In the last 4 years (1937 to 1940) 48 cases in which haemolytic streptococci other than group A were found have been admitted to the unit. They constituted 14.74 per cent of the total cases of haemolytic streptococcal infection admitted during that period. Cases of puerperal sepsis in this unit are divided into two groups, post-partum and post-abortum, according to whether pregnancy terminated before or after the 28th week.

The distribution of the streptococcal infections in the two groups is shown in Table I.

TABLE I

*Table showing incidence of Haemolytic Streptococcal Infections in post-partum and post-abortum sepsis* (1937 *to* 1940)

| | Total cases | Total due to H.S. | Percentage due to H.S. | Total H.S. of groups other than A | Percentage of H.S. other than A to total H.S. | Percentage of H.S. other than A to total cases |
|---|---|---|---|---|---|---|
| Post-partum | 701 | 247 | 35.24 | 23 | 9.31 | 3.28 |
| Post-abortum | 462 | 58 | 12.55 | 25 | 43.10 | 5.41 |

H.S. = haemolytic streptococcus.

The rarity of streptococcal infection in post-abortum cases as shown in the table is probably associated with two main factors: (1) the barrier presented by a relatively intact vaginal epithelium and the highly acid reaction of the vaginal secretion, and (2) the infrequency of attendance of doctor or midwife on such cases with lessened risk of infection from an outside source. That this relative immunity to the streptococcus affects principally group A, is shown by the fact that in the post-abortum series 43.1 per cent of the streptococcal infections were due to streptococci other than group A, compared with 9.3 per cent in the post-partum group.

Table II shows the distribution of post-partum and post-abortum infections when the cases are analysed in groups according to the serological identity of the haemolytic streptococcus and the association or not of the streptococcus with genital tract infection.

TABLE II

| | Post-partum cases | | Post-abortum cases | | |
|---|---|---|---|---|---|
| | Streptococcal infection + | Streptococcal infection D or − | Streptococcal infection + | Streptococcal infection D or − | Total |
| Group B | 2 | 5 | 7 | 2 | 16 |
| Group C | 3 | 3 | 1 | 5 | 12 |
| Group D | 2 | 2 | 1 | 1 | 6 |
| Group G | 5 | 1 | 6 | 0 | 12 |
| Unclassified | 0 | 0 | 2 | 0 | 2 |
| Total | 12 | 11 | 17 | 8 | 48 |

Streptococcal infection + or − = Genital tract infection which could or could not be definitely attributed to the associated streptococcus.

D = doubtful.

## SYMPTOMATOLOGY

*Group B*. There were 16 patients in this group, two of whom proved fatal (cases 1 and 2 already described). Nine of these cases were post-abortum and 7 post-partum. Sepsis of the genital tract was present in 13 of the 16 cases; of the remaining 3 cases the first patient, a post-partum case, had no genital tract sepsis, but had a late puerperal pyrexia associated with urinary infection; in the second patient sepsis had probably been present but considerable treatment was given before admission, and she was practically normal when admitted to the unit; in the third patient, No. 2 of the fatal septicaemias, there was no direct evidence of sepsis of the genital tract. Of the 13 patients with genital tract infection the sepsis could definitely be attributed to the haemolytic streptococcus in 9, and in the others the lochia was markedly offensive. In none of the patients was the infection severe. In one, acute infective arthritis of the right sacro-iliac joint commenced 5 days after an induced abortion. In this case, genital tract sepsis was mild and evidenced only by offensive lochia and a low-grade pyrexia which did not exceed 100°F. and which subsided completely after 6 days in hospital.

Offensive lochia were present in every patient in this group in which there was genital tract sepsis excluding the 2 fatal septicaemic patients. The uterus was bulky or persistently subinvoluted in 4 cases. Offensive retained products were removed from all but one abortion and from one post-partum case. The pyrexia was for the most part mild and of short duration; it reached 105°F. in one patient following removal of retained products, which in itself frequently gives rise to a high reactionary temperature. The average duration of pyrexia was 4 to 6 days, but in one patient there had been pyrexia for 9 days and in another for 6 days before admission.

Leucocytosis was quite a marked feature of these cases. It is difficult to fix an arbitrary dividing line above which the leucocyte count might be taken as pathological, but probably 12,000 per c.mm. may be regarded as an index of some infection. A white cell count was performed in 14 of the 16 cases and in 8 of the patients it exceeded 12,000; in 4 it exceeded 15,000; and in 2 it exceeded 20,000.

*Group G*. There were 12 cases in the group. Two patients died, one from infective endocarditis (case 3 already described) and the other as a result of extensive pelvic peritonitis; 6 of the cases were post-abortum and 6 post-partum. Both the fatal cases

followed induced abortion. Genital tract sepsis was present in all but one, a post-partum infection due to a flare up of chronic sepsis of the urinary tract; there was no sepsis of the genital tract in this patient and the haemolytic streptococcus must be regarded as saprophytic. In two of the post-abortum cases the infection was mild and the sepsis was attributed with some hesitation to the streptococcus; in one of these patients the organism was also recovered from the blood-stream; in the other there were offensive lochia following the passage of a macerated foetus and no other organism was present. Thus the genital tract sepsis present in 11 patients was considered in every case to be attributable to the streptococcus.

Apart from the two fatal cases the infection was mild. One patient developed femoral thrombosis; there was a low-grade pyrexia for 15 days after admission to hospital; swelling of the limb persisted for 24 days and the patient was 53 days in hospital. In 7 patients the uterus was bulky and/or persistently subinvoluted, and in all but one of these the lochia were offensive and purulent. The remaining 4 cases were very mild. The temperature charts showed for the most part a sharp rise to 103° F. or 105° F. with rapid fall to normal after the second day; in 2 patients (apart from those who died) there was a low-grade pyrexia continuing for 10 to 15 days.

The most striking feature of the group G infections was the presence of a high leucocyte count. This had been made in 9 of the 11 cases of genital tract infection due to this organism; in 8 of these 9 cases the white cell count exceeded 12,000, the exception being the fatal case of septicaemia in which the leucocyte response never exceeded 9,800. In 5 of the cases the counts were respectively 22,000, 22,900, 25,800, 28,550 and 33,400. The count of 28,550 occurred in the fatal case of peritonitis; in 3 of the other patients there was marked bulkiness and subinvolution of the uterus with foul purulent lochia, but in the remaining patient who showed the highest count of 33,400 the infection was a mild one with offensive retained products; in this patient the temperature rose to 105° F. at the time of the abortion, settled to normal immediately but rose to 102° F. on the 3rd day, thereafter settling rapidly again. It is difficult to explain this excessive leucocytosis in group G infections, associated as it was with a high proportion of polymorphonuclear cells (above 70 per cent in all 9 cases and between 83 per cent and 90 per cent in 5 of them).

The details regarding the fatal case of pelvic peritonitis were as follows:

Multipara 2, aged 34. Admitted to a L.C.C. hospital on October 3rd, 1939, following a self-induced abortion which had taken place that day. Pyrexia commenced at once with a severe rigor, headache and vomiting. Pyrexia continued and on October 7th the patient was transferred to this unit. On admission she seemed exhausted and was delirious. She complained of recurring attacks of acute lower abdominal pain. The uterus was bulky and there was an extremely tender mass extending along the right wall of the pelvis. The lochia were offensive. By October 12th the mass had spread upwards and was palpable in the right iliac fossa. The patient was still toxic and complaining of constant lower abdominal pain. By October 17th the mass in the right side had localized completely and the patient was markedly jaundiced. On October 19th the os was dilated under general anaesthesia and several ounces of pus escaped from the uterus; an incision was made into the pelvic mass through the posterior vaginal fornix, but pus was not obtained. The patient collapsed 2 hours after the operation; a blood transfusion of 700 c.c. was given but she died 3 hours later.

Post-mortem revealed a sloughy tract ¾ inch above the cervix leading into a large gangrenous mass in which the right ovary, Fallopian tube and broad ligament were all implicated; it was through this that the pus had escaped on dilating the os and this hole had presumably been made when the abortion was induced; the wall of the uterus was completely gangrenous and there was a small perforation through the fundus. There was no thrombosis in the pelvic veins. The spleen was toxic, being soft and diffluent and weighing 9¼ ounces. There were some pleural adhesions on the right side; otherwise the heart and lungs were normal. The liver was large. There was a small embolic lesion in the pons.

Bacillus coli and haemolytic streptococci were grown both from the cervix and the urine; blood culture was sterile. The haemolytic streptococci were shown to belong to group G.

*Group C.* This group consisted of 12 cases. All were mild and none proved fatal. Six were post-partum and 6 post-abortum. In 4 of the patients there was no clinical evidence of any sepsis of the genital tract. In only 4 of the remaining 8 patients could we definitely attribute the infection to the streptococcus. In all these 4 patients the uterus was thickened or subinvoluted and in 2 the lochia were purulent and offensive. Pyrexia was mild and low-grade and varied between 4 and 11 days in duration.

White cell counts carried out in 10 of the cases showed a tendency to rise but not to the extent seen in group G or even in group B; in 5 it exceeded 12,000 but no case was above 15,000.

The strains of haemolytic streptococcus from 6 cases were tested for their fermentation of trehalose and sorbitol; in fermenting trehalose but not sorbitol all the strains were shown to belong to the type of group C streptococcus commonly isolated from human sources.

*Group D.* Group D haemolytic streptococci are excluded by some workers from the true haemolytic streptococci, and Graham and Bartley[8] have lately shown that they are identical, save in their production of haemolysis, with the enterococcus or str. faecalis. Evidence as to their pathogenicity is not convincing. Taylor and Wright isolated pseudo-haemolytic streptococci (probably group D) from 1.9 per cent of patients before delivery but found no evidence that they could give rise to infection in the puerperium. Of 837 women examined by Hare and Colebrook[9] after delivery, 34 showed pseudo-haemolytic streptococci and 27 of these had a nonfebrile puerperium. They stated that: "Seven of the 34 women from whom these organisms were isolated had low-grade fever during the puerperium, and there is the possibility that this may have been caused by the presence of these organisms, but it is necessary to add that in only a few instances were the organisms isolated in pure culture and all the women except one had a difficult labour, intra-uterine operations being necessary. It is possible that anaerobic streptococci which were usually associated with them in culture may have been in part responsible for the elevation in temperature."

In the present study there were 6 patients (four post-partum and 2 post-abortum) from whom group D organisms were isolated. In 3 of them there was a spread of infection beyond the uterus but it is difficult to say whether the group D organism was responsible; no other organism was isolated in any of the 3 cases.

The details of the two chief cases are as follows:

(1) Multipara 2, aged 31. Normal delivery January 15th, 1937. Pyrexia commenced January 19th; rigors occurred on January 19th and January 21st. The patient vomited and complained of pain on micturition. She was admitted to the unit on January 24th. On admission the cervix was lacerated and patulous and very unhealthy with glairy mucoid discharge from the external os; the uterus was enlarged and there was a very tender hard ridge in the base of the broad ligament on the left side. Two days after admission bronchitis developed. The abdomen was distended and slightly tender on the right side. The condition became worse, and on January 28th there were signs of extensive consolidation in the right lower lobe and pleural

friction rub was present. By January 30th both bases were stony dull. Aspiration failed to reveal the presence of fluid. The general condition became worse and the temperature which had so far been low-grade began to rise. Death supervened on February 5th, after an illness of 17 days.

The bacteriological findings were as follows: Haemolytic streptococci group D were isolated from both cervix and blood (less than 1 organism per c.c.) on January 25th. On January 30th blood culture was sterile. Urine was sterile on January 25th, but not on January 31st, when an enterococcus grew on culture and numerous pus cells were present. A white cell count on February 1st showed 34,000 white cells with 93 per cent polymorphs.

The post-mortem report was as follows: There was sero-purulent fluid in the right pleural cavity with adhesions over the right middle and lower lobes; fibrinous exudate over the right middle lobe extended into the interlobar space between the middle and lower lobes; there was early pleurisy over the left lower lobe. The right lung showed generalized broncho-pneumonia of an advanced stage with extensive oedema and the left lower lobe showed early broncho-pneumonia. The heart was normal. The peritoneal cavity contained an excess of sero-purulent fluid becoming fibrinous in the pelvis. There were adhesions of bowel to the anterior abdominal wall and fibrinous matting in the pelvis. The greater part of the small bowel was distended. The liver was enlarged and adherent to the diaphragm; the cut surface was pale. The spleen was enlarged, soft, red and diffluent. The cut surface of the kidneys was pale and the pelvis and ureters slightly dilated. The uterus was subinvoluted and the cervix red and covered with inflammatory exudate. The endometrium was slightly inflamed. The right Fallopian tube was healthy but the left had catarrhal exudate in the lumen. The ovaries were healthy. Bacteriological examinations were not made post-mortem.

(2) Multipara 2, aged 34. A 12-week abortion occurred on January 11th, 1937. Pyrexia and pain in the left iliac fossa ensued. She was admitted to the unit on January 17th. On examination the cervix was found to be inflamed and lacerated; the uterus was enlarged and there was a ridge of pelvic cellulitis extending along the base of the broad ligament on the left side which was tender on pressure. The temperature varied between 100°F. and 103°F. for the first 7 days after admission; thereafter it gradually settled to normal, and after the 14th day in hospital there was no recurrence of pyrexia. The cellulitic mass gradually became absorbed and the patient made an uneventful recovery. She was discharged on February 20th, after 34 days in hospital. Haemolytic streptococci group D were isolated from the cervix on both January 18th and January 19th. Urine and blood cultures were sterile.

A third patient was admitted with profuse purulent discharge and a bulky uterus which remained subinvoluted for 11 or 12 days after admission. During this time there was a low-grade pyrexia which never exceeded 100°F. and settled finally to normal 17 days after admission. A pure culture of haemolytic streptococci group D was obtained from the cervix on admission.

In the remaining patients from whose genital tract group D haemolytic streptococci were isolated the sepsis could not be attributed to these organisms. In two of them there was sepsis of the urinary tract, and the third left hospital after 2 days against advice and before investigation was complete; a pure culture of haemolytic streptococci group D had been obtained from the cervix on admission.

The strains from 2 cases were unclassified. They were negative to Lancefield groups A, B, C and G. Infection in both patients followed abortion and in both there was definite genital tract sepsis. In neither case was a pure culture of the streptococcus obtained from the cervical swab; diphtheroids were present in one and diphtheroids and b. coli in the other. In the first patient there was a swinging temperature for 5 days and this did not settle completely until after the 10th day; pus cells or organisms were not present in the urine. In the second patient removal of retained products had twice been performed following an abortion which occurred 23 days before admission to hospital. During this time there had been irregular bouts of pyrexia and this persisted for 12 days after admission though never exceeding 100°F. There was little or no evidence of sepsis in either the genital or urinary tracts. The streptococcus was obtained from the genital tract both before and after admission and together with b. coli was also found in the urine.

*Source of organisms.* Unfortunately very little light can be thrown on this important aspect from the present study. Although nose and throat swabs were taken from every patient on admission, haemolytic streptococci were isolated from the throats of only 3 patients. In one of these, the streptococcus could not be grouped; in the second, a group C streptococcus (Griffith's type 20) was isolated from both throat and cervix; and in the third, a group G streptococcus was isolated from the throat and a group D from the cervix. It seems likely that the group C and G strains come from the throat of some attendant human carrier, while the group B and D strains may already be present in the genital tract before confinement or abortion.

*Lancefield test*: Fuller's (1938) formamide method for the Lancefield group test has been used since its introduction. It has the advantage over the older acid-extraction method that only 5 c.c. of glucose-broth culture is needed, and in our experience it has given better readings than did the older method. We use the precipitation ring-test in a capillary tube. The precipitating sera were prepared in rabbits given two or more courses of a

vaccine of group A, B, C and G streptococci respectively. The response in individual rabbits varied considerably. Care must be taken to see that a particular precipitating serum does not give cross-reactions with other groups; for example, the group A streptococcus extract has sometimes given a delayed positive reaction with our group G serum. Strains which failed to react with any of these four sera were tested for soluble haemolysin and heat-resistance. If the former test was negative and the strain resisted a temperature of 60°C. for half an hour, it was regarded as a group D or haemolytic enterococcus.

## Discussion

From the foregoing analysis and the findings of other writers it would appear that some modification must be made in our view of the relative pathogenicity of the various groups of haemolytic streptococci in puerperal sepsis. It may be stated (1) that group A are not the only haemolytic streptococci associated with severe infections, and (2) that, contrary to the statement of Lancefield and Hare that "Group A haemolytic streptococci if present in the vagina post-partum almost always give rise to serious puerperal infection", these organisms may frequently be grown in pure culture from cervical swabs of only mildly infected cases.

(1) The most striking characteristic of the severe and fatal infections of the other-than-A groups has been the occurrence of bacterial endocarditis. Our own cases and those reported by Fry, Hill and Butler, and Macdonald, show that strains of haemolytic streptococci belonging to groups B and G have an affinity for the heart valves, producing an infection intermediate in its virulence between acute ulcerative endocarditis and subacute bacterial endocarditis. In contrast to the latter a pre-existing cardiac lesion is not apparently necessary. The post-mortem findings in our group B cases were similar to those described by Fry and Hill and Butler. The vegetations on the mitral valve were large and consisted of a massive deposit of thrombus with surface ulceration. It has been suggested by Fry that this large amount of thrombus is due to the absence of fibrinolysin in group B haemolytic streptococci, and he cites in contrast a case of endocarditis due to the fibrinolytic group A haemolytic streptococcus where the vegetations were merely small raised plaques. Fry's cases were both post-partum. Hill's and Butler's cases were post-abortum: one of ours was post-

partum and one post-abortum. The duration of illness in our patients was 48 and 111 days compared with 28 and 26 in Fry's and 27 and 15 in Hill and Butler's. In our first patient a genital origin is suggested from the fact that the infection began a few days after abortion while one colony of haemolytic streptococcus group B was recovered from the cervical swab on admission to this unit 28 days after abortion had taken place. In the second patient the genital origin, though presumptive, cannot be proved. Fry considered a genital origin unlikely in his cases but, as Hill and Butler pointed out, the first vaginal cultures were not made until the 17th and 18th days of the puerperium, by which time the initial genital infection might easily have subsided.

In Macdonald's two fatal cases of group G endocarditis the vegetations on the mitral valve were small raised plaques similar to those described by Fry as typical of fibrinolytic group A infection. One of Macdonald's strains was weakly fibrinolytic, the other (tested after 10 years) was non-fibrinolytic. The group G streptococcus as a rule resembles group A in producing fibrinolysin. In our case the vegetations were quite large but less solid and bulky than those in the group B infections.

(2) As regards the severity of group A infections, a survey of 2 different years, 1932 (before the introduction of sulphanilamide therapy) and 1940, shows that in 1932 when septicaemia and peritonitis were not uncommon group A haemolytic streptococci were obtained in pure culture from cervical swabs in 47 mildly infected cases. During the past year only 3 out of 44 cases of infection with group A haemolytic streptococci admitted to this unit were in any way serious infections. In 34 cases the disease was very mild and in all pyrexia had completely settled within 7 days of admission to hospital. Nine cases were not treated with the sulphonamide drugs.

A comparison between mild infections due to group A haemolytic streptococci and mild infections due to the other groups showed few marked differences. Apart from offensive lochia in the other-than-A cases the clinical signs and course of the disease were very similar. The leucocyte response, marked in group G infections, was moderate in group A and B infections, and practically absent in the group C cases. That the group C streptococcus can cause more acute infection than was encountered in this series, however, was instanced by the puerperal case quoted by Hill and Butler, and is supported by our own experience with throat infections.

SUMMARY

1. Three fatal cases of puerperal infection in which the cause of death was subacute endocarditis due, in two cases, to Lancefield's group B and in one to group G haemolytic streptococcus, are described. The clinical course and post-mortem findings in these patients are compared with those of 6 similar cases reported in the literature.*

2. An analysis has been made of 48 cases of infections due to haemolytic streptococci of groups other than Lancefield's group A, admitted to a puerperal sepsis unit during the 4 years 1937-40. Although streptococcal infection was much less common after abortion than full-time delivery (in this series 12.5 and 35.2 per cent respectively of all admissions), streptococci of groups other than A were isolated from a much higher proportion of post-abortum than of post-partum streptococcal infections, viz. 43.1 per cent compared with 9.3 per cent.

3. Puerperal infection with streptococci other than group A is usually mild and does not differ much from mild group A streptococcal infection which forms a high proportion of the streptococcal puerperal infections admitted to this unit.

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* After the completion of this article a report of two further cases of fatal puerperal streptococcal endocarditis was noted (Rosenthal, A. H., and F. M. Stone, *Journ. Amer. Med. Assoc.*, 1940, cxiv, 840). Group B and group C haemolytic streptococci were the causative organisms and large crumbling vegetations were found on the mitral valves in both cases. The authors believe that the group C endocarditis is the first fatal case reported. Massive doses of sulphanilamide failed to save the patients.

# The Posterior Pituitary Factor in Toxaemias of Pregnancy*

BY

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## INTRODUCTION

"TOXAEMIA of pregnancy is a disease of theories." It has long been believed that the symptoms in pregnancy toxaemia could be explained on the assumption of a toxin circulating in the maternal blood, although the very word toxin appears to be only a means of concealing our inadequate knowledge on the true nature of the causative agent. However ample the biological experiments by several observers may be the results are often contradictory. The consequential uncertitude on the nature of this toxin entails difficulty in ascertaining the source and formation of such a substance. As can be expected in the circumstances, both the mother and baby have been supposed to be causes in producing the toxin, and the placenta has also been said to be involved in some cases.

With the advent of modern knowledge of endocrinology attention has been withdrawn to some extent from the foetus and placenta to the endocrine glands of the mother. Here again we find ourselves in unexplored territory. The correlation between the different endocrine glands is still remote from discovery, much more so the alterations in their functions during pregnancy. Pregnancy further burdens the metabolic balance of the mother, and so long as the normal state of the maintenance of metabolic equilibrium is a quandary it is hard to judge the nature and extent of the abnormality caused by pregnancy in these patients. However, one prominent feature is that every pregnant individual is not a victim of toxaemia, and she who is a prey in one pregnancy does not always display a repetition of like symptoms in subsequent pregnancies. The manifestations of toxaemia of pregnancy are varied, yet they have one property

* Thesis for the degree of Mastership of Obstetrics Examination, University of Calcutta. By permission of the University.

in common, namely, conception. The query that confronts one is whether the pregnancy affects the maternal system in the same or in a solely different way in different individuals. If the foundations of this abnormality be identical in all, why are their manifestations so variable? If the underlying factor is dissimilar in each individual, why this dissimilarity? Unfortunately, the facts available at present do not offer satisfactory answers to our whys and wherefores.

As time passes the latest speculations are accepted on trial, but some theories have already been discarded, while others are fading into obliteration. On summarizing the symptoms of pregnancy toxaemias we find some common to all, namely, alterations in the normal cardio-vascular physiology, and renal secretory functions, but the nature and extent of these vary, and some association of a disorder of the hepatic function is frequent. Strenuous efforts have been made to interrelate these differences, but in the last 25 years our endeavours have advanced little.

When the endocrines in the normal metabolism were being divined Hofbauer[1] tried to postulate an endocrine basis for the toxaemias of pregnancy. The posterior lobe of the pituitary and the adrenal glands together maintain the normal vascular tone and blood-pressure of the human body. He, therefore, inclined to a belief that pregnancy toxaemia was a sequel to the disturbance of the neuro-hypo-physeo-adrenal equilibrium. This theory was easily understood but difficult to explain. Why should pregnancy affect the equilibrium between the hypophysis and adrenal on the one hand, and the cardio-vascular system on the other? How do we account for this disturbance affecting only a selected group of pregnant mothers and not all? To these questions there was no satisfactory answer in 1918 when this theory was advanced. To explain his theory further Hofbauer[2] later brought forward a very ingenious suggestion, that placental biogenous amines are absorbed into the maternal system from minute degenerative foci in the placenta and affect this hypo-physeo-adrenal system. The latter part of Hofbauer's theory, because of its close resemblance to Young's[3] conception of pregnancy toxaemia, gained considerable popularity, yet his former theory pertaining to the neuro-hypophysis and suprarenal has not met with general approval. Ten years after Hofbauer's speculation on the endocrines in the toxaemias of pregnancy, Kustner[4] related his findings in the blood of eclamptic patients. As a result of his experiments he held that the blood of these

patients contained a substance which would stimulate expansion of melanophores in the frog. The only substance which produces a definite melanophoric response in these animals is the hormone of the posterior lobe of the pituitary body. Thus Kustner's theory and findings supported in some measure the preceding contribution of Hofbauer. From the conclusions arrived at by these workers it appears that the posterior pituitary body, either directly or indirectly, bears a relation to the toxaemias of pregnancy.

From 1928 to 1932 there was no advance on the conceptions of Hofbauer and Kustner, but in 1932 Anselmino, Hoffmann, and Kennedy[5] published their article on the relation of hyperfunction of the neuro-hypophysis to eclampsia. They employed blood ultrafiltrates for their experiments, which were confined chiefly to the determination of antidiuretic and pressor effects. It seems worthwhile to quote a few lines from their experiences in this direction:

"For the last 30 years research has been chiefly directed to a search for the toxin of the worst form of toxicoses, namely eclampsia . . . we prefer to study the less severe cases with a view to elucidating the metabolic disturbances on which the toxicoses depend . . . which is best exemplified in the pre-eclamptic states, that is in patients with dropsy and nephropathy. . . . The main metabolic upset in such cases is the tendency to water retention. . . . When the pregnancy toxicoses are included among endocrine disorders it is at once recalled that the cardinal symptom of water retention can be duplicated by the characteristic pharmacological action of the posterior hypophysial autacoid, which acts apparently by causing increased absorption in the tubules. . . . Chronic pituitrin poisoning of rabbits gave a typical picture with cloudy swelling and fatty degeneration of the tubules, and some glomerular change. . . .

"The second feature of the toxicoses that springs to mind is the very frequent rise in blood-pressure, and this too corresponds with the vaso-pressor component of pituitrin. . . . Rowntree produced coma and fits in rabbits by combined pituitrin and water poisoning, which appear to have been much like eclampsia. Lung oedema is a characteristic post-mortem appearance in eclampsia, and animals poisoned by large doses of pituitrin show marked oedema of the lungs. . . ."

These authors were able to detect experimentally an increased content of the posterior pituitary hormone in the blood

of most of their cases. Zangemeister,[6] although his suggestion was not appreciated at the time, had previously propounded the theory that in toxic albuminuria a slowly increasing production of antidiuretic substance associated with proportionate diminished secretion of thyroxin was followed by water retention, the site of action of these substances being the renal tubules. There is no question now regarding the antidiuretic property of the posterior pituitary autacoid, although an explanation for the diminished thyroxin secretion is much less perfectly understood. The ionic distribution of the sodium chloride appears to be sufficient ground on which to explain the oedema of the tissues, even leading on to an alteration of the intercranial tension to precipitate the final stroke, namely, eclampsia. Volhard[7] tried to solve the problem from the point of view of the pressor autacoid of the posterior pituitary, so much so that an eclamptic attack might be explained by Volhard's suggestion on the assumption of vaso-constriction of the cerebral vessels; incidentally this theory is also supported by Stroganoff.[8] In spite of the sporadic efforts of these and other observers the question of pregnancy toxaemia was more or less left unanswered until the investigations of Anselmino, Hoffmann, and Kennedy were published.

Harvey Cushing[9] in 1933 carried on some anatomical investigations to prove the functional activity of the neuro-hypophysis (pars hypophysis posterior). His work was based on the investigations of Zondek and Krohn,[10] who showed that a melanophore expanding substance was abundantly found in the extracts from pars intermedia, stalk and tuber. Cushing demonstrated that when the normal activity of the pars intermedia was exaggerated in pathologic states there occurred marked hyperplasia of the basophilic elements. Not only did these elements discharge their secretory products into the relic of residual cleft, but the ripened element wandered deeply into the neural tissue after the manner of malignant epithelial inversion. The infiltrating elements were accompanied by a great increase in the hyalinoid secretory product. The impression from this appearance was that this secretion was forcing the cells apart in being extruded into the ventricle. A few fatal cases of eclampsia were examined by this observer, and he found that in these cases the pituitary glands showed massive basophilia of the pars nervosa. This work was further continued by Harvey Cushing,[11] and his observations published in 1934 appeared extremely interesting. He describes the post-mortem

appearances of 9 cases of eclampsia with particular reference to hyperactivation of the neuro-hypophysis. It is evident from this series of cases that the basophilic invasion was to some extent proportional to the degree of hypertension. In one patient there was slight invasion only, and her blood-pressure was 130/90 mm. Hg. In 6 of his cases the history was typical, and infiltration excessive. In 1 case of questionable eclampsia, in spite of a systolic pressure of 170 mm. Hg, basophilic invasion was not noticed.

Continuing the work of Cushing, Ählström[12] commenced the study of basophilic infiltration of the neuro-hypophysis. He examined 61 specimens from eclampsia patients, of these 36 patients were without any hypertension, whereas 25 were subject to varying degrees of hypertension. It was found that 18 out of 36 of the non-hypertensive group and 24 from the hypertensive group showed basophilic infiltration of the pars nervosa. The extent of basophilia was variable, in 14 cases of the whole group this was considered severe. Ählström, however, could not come to a definite conclusion on his results, although he tried to establish a relation between the pituitary gland and toxaemias of pregnancy. His inability to arrive at a conclusion was due to his finding basophilic invasion in the non-hypertensive cases of eclampsia. Ählström's observations were not absolutely in agreement with Cushing's discoveries, for the reason that most of Cushing's cases were associated with hypertension, whereas Ählström's were almost equally divided between hypertensive and non-hypertensive cases. This author apparently overlooked the fact that the pituitary autacoid consisted not only of a vasopressor substance but also of an antidiuretic and a melanophore expanding hormone. The patients in whom hypertension was not well marked revealed remarkable oliguria with retention of chlorides and oedema. The basophilic invasion of the posterior pituitary may explain the diminution of urinary output in these cases, just as both hypertension and oliguria can be cleared by the explanation of the same finding in the other group.

From the above investigations one can obtain a glimpse at the posterior pituitary factor in the aetiology of toxaemias of pregnancy, but, unfortunately, the results and interpretation of results are far from convincing. Due to the difficulty in procuring post-mortem specimens from suitable subjects of toxaemia of pregnancy Cushing's and Ählström's observations could not be corroborated. The present observer had, therefore, to content himself with biological and biochemical investigations, to some

extent similar to those of Anselmino *et al.* The outcome of his research is detailed below.

## Basis of Investigation

Presuming that a posterior pituitary factor exists in the development of toxaemia during pregnancy the following facts are to be expected:

1. The posterior pituitary hormone being secreted in the third ventricle through the tuber is absorbed by the choroid plexus and the *tela choroidea* of the third ventricle and distributed to the circulation. This may be the reason why Levitt[13] and others who experimented with cerebro-spinal fluid obtained from the caudal region of the subarachnoid space, found that it partly failed to act, although with the use of blood ultrafiltrates fairly satisfactory response was secured.

2. The pituitary autacoid (with its complex properties) after absorption shows a dual response in human beings, namely, vaso-pressor effect and antidiuretic effect, whereas in amphibia a third type of action (dilation and expansion of the melanophores) may be obtained. The intensity of vaso-pressor and antidiuretic effects do not run collaterally, for in some patients hypertension without considerable oliguria may be the impressionable feature, while in others normal arterial tension may be accompanied by considerable lessening of the urinary output. Why this should be so is difficult to explain, and although this lack of parallelism has been observed between the antidiuretic and vaso-pressor effects of the filtrates it has not yet been explained. It can be anticipated that further experiments will help us to deduct a more satisfying explanation on this subject.

## Materials and Data

As sufficient concentration of the posterior pituitary autacoid cannot be expected in the cerebro-spinal fluid obtained from a region beyond the third ventricle, attempts have not been made to carry on investigations with cerebro-spinal fluid. A few preliminary observations were made with extracts from blood, isolated by chemical precipitation of serum proteins and fractional separation of lipoids, and maintaining the extract at a *p*H of 5 to 5.5. These extracts unfortunately could not be freed completely of amines which gave an anomalous response. Further experiments were, therefore, conducted with ultrafiltrates of blood. Thirty c.c. of citrated blood (blood to which

2 c.c. of $2\frac{1}{2}$ per cent sodii citrate in normal saline has been added) were collected from the antecubital vein. The blood was centrifugalized and plasma decanted off; 13 to 15 c.c. of clear plasma could be obtained in this way. As the pressor and antidiuretic hormones rapidly deteriorate in an alkaline medium, the plasma was acidulated with $1\frac{1}{2}$ to 2 c.c. of N/150 acetic acid and a buffer solution added to prevent alteration of reaction. Plasma was then filtered through a collodion filter-bag of $\frac{1}{2}$ mm. thickness under pressure. This was, however, a time-consuming process, but approximately 7 to 8 c.c. of filtrate could be obtained in this way. As soon as the filtrate was visaged it was tested colorimetrically for its *p*H. A *p*H of 5 to 5.5 has been found to be optimum, and could be judged fairly satisfactorily by a universal indicator. The *p*H was adjusted by adding the requisite quantity of N/300 acetic acid or sodium hydroxide. The filtrate was tested for protein and amine reactions; if they were negative it was evaporated *in vacuo* (to 2 c.c.), fractionally sterilized, and sealed in ampoules for future use. It seemed to be fairly stable when kept on ice.

## Cases Investigated

The total number of cases selected for biological investigation was 50. The cases were chosen from an unselected group of patients without any regard to the intensity and nature of toxaemia or their age and parity. They may, however, be classified under the following heads: Eclampsia, 2; pre-eclampsia, 40; nephritic toxaemia, 1; accidental haemorrhage, 3; hyperemesis gravidarum, 4.

The material obtained for the purpose of investigation was always secured before any treatment was given to these patients. Of the pre-eclamptic patients 4 had been receiving treatment in the antenatal clinic, and in these, to avoid vitiated results, treatment was suspended for 48 hours before blood was collected. The case of nephritic toxaemia was diagnosed by renal function tests, urinary findings, and biochemical examination of blood. To eliminate neurotic and reflex type of vomiting only well-marked cases of toxic hyperemesis were included. This may explain the apparently small number of cases in this group.

In interpreting the results of biological investigations, the clinical manifestations have been compared with the experimental findings. An analysis of the principal features thus appears to be important. The chief manifestations of pregnancy

toxaemia may be looked upon as: (1) Hypertension and (2) oliguria and renal disfunction.

Hypertension was the outstanding symptom in 24 cases. The majority of the patients with hypertension, however, were found to have a certain degree of renal disfunction, as manifested by oliguria, albuminuria, and sometimes acetonuria. Two patients in this group had hypertension as the only important manifestation without any evidence of toxic impairment of the renal secretory functions. In 26 patients hypertension was absent, and the main feature in this group was oliguria with varying degrees of albuminuria. In 5 out of these 26 patients albuminuria was very marked, the urine becoming solid on boiling. Advances have not been made to correlate subjective symptoms with biological findings, as it is well understood that the subjective symptoms are only external manifestations of a deeper pathological lesion.

It will appear from the results of investigations noted in the succeeding pages that attempts have not been made to interpret the results in accordance with the types of toxaemia. Toxaemia of pregnancy the author considers one underlying disease, the different manifestations of which become evident in different conditions. An analogy of a similar condition may be found in general medicine when rheumatic fever, tonsillitis and chorea are included under the heading of rheumatic infection (or rheumatism). In the present series of investigations attempt has been made to arrive at one causative factor for pregnancy toxaemia, which is intrinsically one disease with varied manifestations.

## Biological Investigations

Biological experiments can conveniently be classified under three headings:

1. Melanophoric response.
2. Antidiuretic effect.
3. Vaso-pressor effect.

### *Melanophoric Response.*

The frog has been found to be the most useful animal in exhibiting the melanophoric response. *Rana esculanta* shows the effects best, but unfortunately this species of rana is unobtainable in this country. So *bufo melanostictus* and *rana temporaria* were chosen for this experiment. It has been the view of Teague,

Noojin, and Geiling[15] that hypophysectomized frogs show the response more effectively than intact animals, but in the hands of the observer the response of these varieties of frogs did not seem to vary to any considerable extent. The expansion of melanophores could be detected with the naked eye on the back and hind limbs, but under microscopical examination of the web of the foot of a pithed frog this expansion displayed a most interesting picture. Every experiment was worked with two animals. To each animal 1 c.c. of sterile saline was injected and the melanophores watched, both with naked eye and under the microscope. No change was noticed in any one of them. To one animal 2 c.c. of the toxic ultrafiltrate was injected, and to another an equivalent amount of ultrafiltrate from the normal pregnant individuals after a lapse of 15 minutes. All the injections were administered in the dorsal lymph sac.

*Results.* Within 3 minutes the melanophores of the frogs were seen under the microscope, to dilate, expand, and emit fine processes from their periphery on the reception of the filtrate from the toxaemia patient, while no remarkable or only very slight expansion of melanophores in the control animals receiving the toxic ultrafiltrate could be seen to become darker. The expansion of melanophores and the darkening of the skin reached the maximum 5 to 7 minutes after the injection, and after about 15 to 20 minutes it gradually faded until the normal colour was regained in near 40 minutes. As the melanophoric response reached maximum the whole animals were found to be lying listless, but with the return of their colour their normal vigour was restored. Incidentally it may be mentioned that with $\frac{1}{4}$ c.c. or $2\frac{1}{2}$ Voigtlin units of known posterior pituitary extract (P. D. & Co.) the mode of reaction in the animals was the same both with respect to their general state as well as to their melanophoric response.

For the purpose of observing the melanophoric response in the present series 50 toxic filtrates were examined and controlled by the same number of filtrates obtained from clinically normal pregnant women. The investigation was carried out from an unselected group of cases, so that the degree and intensity of toxaemia varied in different instances. The response obtained was classified into 4 groups—mild, moderate, marked, and absent. In the present series of cases the results were: Mild, in 7 cases, 14 per cent; moderate, in 22 cases, 44 per cent; marked, in 19 cases, 38 per cent; absent, in 2 cases, 4 per cent. It thus appears that in 41 out of 50 cases a fair melanophoric response

was obtained. The extent of melanophoric response was found to follow closely the clinical severity of the toxaemia, but did not bear a very definite proportional relation to the degree of hypertension present. In only 6 out of 24 hypertensive cases of toxaemia was the response marked, whereas in all the rest only a moderate response was noted. A certain amount of dissociation of melanophore expanding and vaso-pressor functions of the posterior pituitary autacoid may thus be evident. It is, however, of considerable interest to note that in none of the hypertensive cases of toxaemia was the melanophoric response mild or absent. An effort was made to combine some relation between the extent of oliguria and melanophoric property of the filtrate. Although this could not be established absolutely, it is worthy of note that in every patient in whom the daily output of urine was less than 22 ounces, accompanied by albuminuria, marked or moderate melanophoric response was noted. Melanophoric reaction was present in 4 patients with marked hypertension even in absence of oliguria and albuminuria, just as in 6 patients with marked oliguria and albuminuria this response was obtained in spite of the blood-pressure being normal. Under the heading of hypertensive cases all patients with blood-pressure of 140 mm. Hg or over of systolic and/or 110 mm. Hg or over of diastolic pressure were included. It is extremely interesting to note that intense melanophoric response was more constant with a high diastolic than with a proportionately high systolic pressure. This seems in accordance with the theory of hyperactivation of the posterior pituitary in pregnancy toxaemias, because it has long been known that the posterior pituitary autacoid raised the blood-pressure by its peripheral vaso-constrictor action. It was observed in the present series of experiments that melanophoric response increased definitely as the diastolic blood-pressure rose. For each 5 mm. rise above 110, an appreciable change in the size of the melanophores of the animals treated with ultrafiltrate could be seen under the microscope in all the 6 cases in which marked response was obtained. To the naked eye, however, such delicate differences were hard to determine. Another important point to note is that although albuminuria and oliguria often go hand in hand, yet the degree of albuminuria has very little to do with the intensity of melanophoric response obtained with the ultrafiltrate. Thus 4 patients, whose urine was solid with albumin on boiling, gave only a mild response. On the other hand, in the presence of all the 3 factors, namely, albuminuria, hypertension, and oliguria, a marked response

could usually be expected. It has been the experience of the author that a positive melanophoric response may usually be obtained 24 to 48 hours before any clinical evidence of fluid retention and oedema is apparent.

*Antidiuretic Effect.*

Anaesthetized animals behave differently from normal animals under the influence of posterior pituitary hormone. Sharpey Schäfer[14] pointed out that pituitary hormone had a diuretic effect on anaesthetized cats, while the same on unanaesthetized animals exhibited an antidiuretic property. These apparent changes in the behaviour of animals in different circumstances make experimental determination of the nature and amount of the antidiuretic substance in the circulation of toxaemia patients a difficult problem.

Female guinea-pigs were found to be fairly suitable animals for testing the antidiuretic property of the ultrafiltrate. The bladder of these animals can be completely emptied by holding them vertically and applying pressure above the pubis. This method of investigation may appear to be somewhat crude, but the author has been convinced that fairly satisfactory and consistent results can be obtained by this procedure. The same ultrafiltrate was used for the investigation. For 2 hours before the experiment was started the animals were starved. Four animals of approximately the same weight were required for each testing, 2 of them serving as controls. Immediately before the study was commenced the bladder of each animal was completely emptied. Injections were given subcutaneously in the abdomen, 2 c.c. of toxic ultrafiltrate in 2 animals, and the same quantity of normal saline and normal filtrate in the 2 controls. The urine from the bladder was collected at intervals of 15 minutes for $2\frac{1}{2}$ to 3 hours from each of the 4 animals separately and measured.

*Results.* It was found that the urinary secretion in the controls did not show any appreciable alteration during the period of investigation. The animals receiving the toxic filtrate, however, behaved in a characteristically different manner. For the first quarter both the sets of animals reacted in a similar way. Half an hour after injection was given antidiuresis commenced in the treated guinea-pigs. This increased progressively and touched maximum 60 to 75 minutes after injection. The effect began to decline about 15 to 20 minutes after the maximum had been attained, and normal condition was regained in about

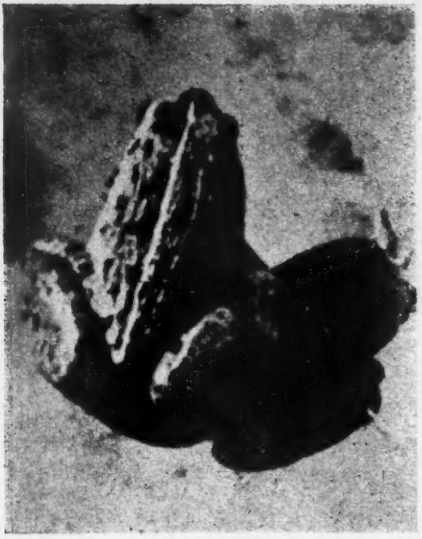

FIG. 1.

Rana temporaria. This animal was treated with normal saline and then with "normal" ultrafiltrate. There was no change in the size of the melanophores in either case.

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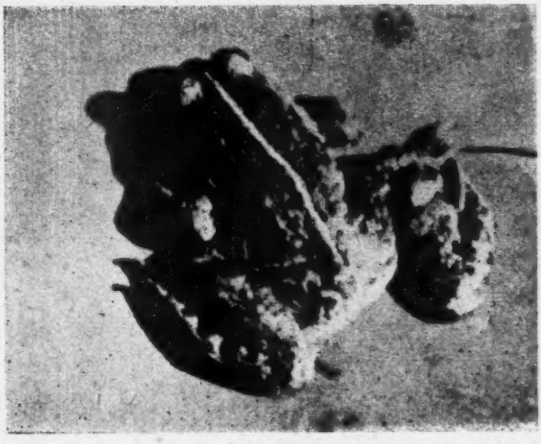

FIG. 2.

"Mild" melanophoric response, showing slight but definite intensification of the dark stripes. Generalized darkening of the skin is not evident.

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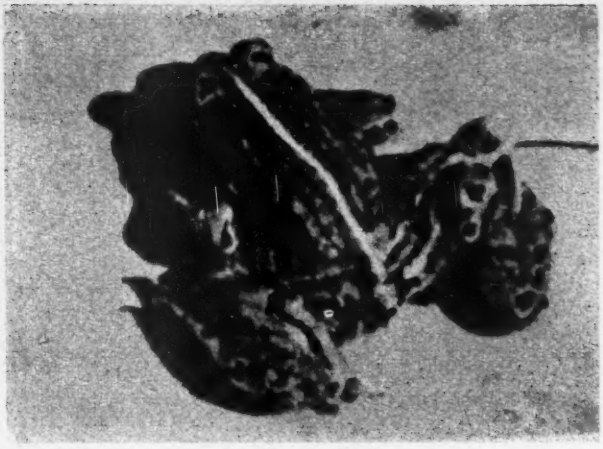

FIG. 3.

"Moderate" melanophoric response, showing more marked intensification of dark stripes. Definite generalized darkening of the skin is also evident. The filtrate was obtained from a pre-eclamptic subject carrying 32 weeks with albumin ++, and blood-pressure 148/110. This patient subsequently developed accidental haemorrhage.

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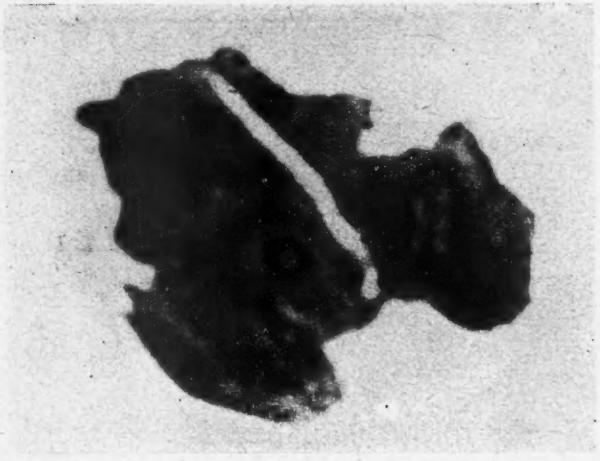

FIG. 4.

"Marked" melanophoric response, showing complete darkening of the skin. Note the listless attitude of the animal. The filtrate was obtained from a bad case of hyperemesis gravidarum. It is of interest to note that in spite of treatment the patient died of complete suppression of the urine. The same ultrafiltrate also gave "marked" antidiuretic, and "moderate" vaso-pressor reaction, although the blood-pressure of the patient at the time blood was obtained for examination was only 98/62 mm. Hg.

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FIG. 5.

" Mild " vaso-pressor response. Chloralosed cat, carotid pressure. Control with " normal " filtrate caused only an insignificant rise of pressure; this is not more than that obtained with saline.

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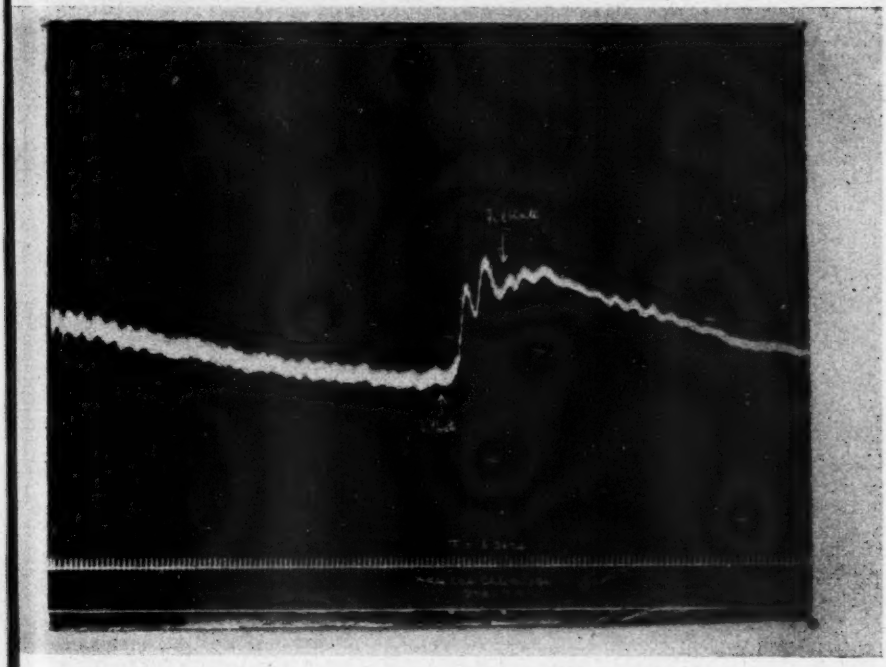

FIG. 6.

" Moderate " vaso-pressor response. As in the previous case the second dose of filtrate had practically no effect on the pressure curve. Such a reaction is characteristic of the vaso-pressor hormone of the posterior pituitary.

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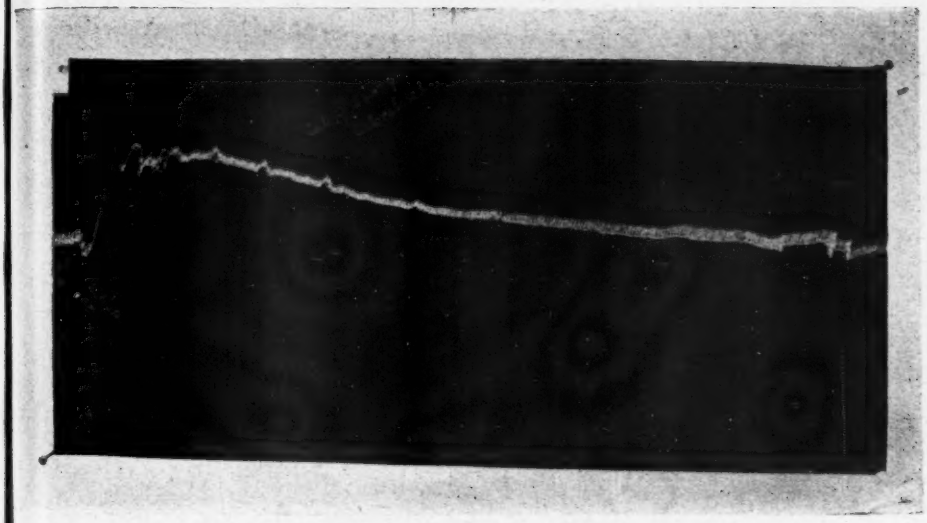

FIG. 7.

"Marked" vaso-pressor response. Even after 25 minutes the pressure curve has not touched the normal level. It will be of interest to note that residual albuminuria (without any impairment of renal function—"delayed healing" of Kobes) and hypertension persisted even 5 months after confinement in spite of intensive treatment. It will be of further interest to observe that the mother of the patient had eclampsia twice, and her only married sister had the same fate during her first pregnancy, to which she succumbed (familial tendency?).

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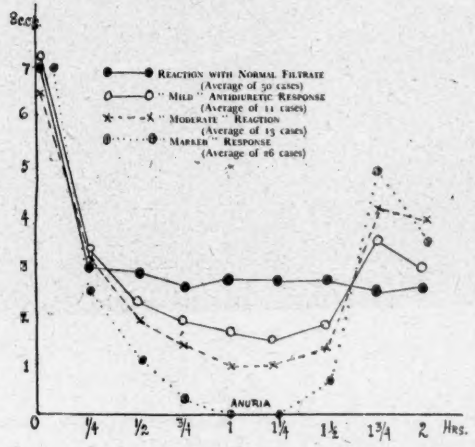


FIG. 8.

**Curve of urinary secretion of guinea-pig, showing response after " normal filtrate," " mild," " moderate," and " marked " antidiuretic effect. A superimposed curve. Note that in the case marked reaction temporary anuria supervened.**

2¼ hours after the commencement of experiment. A period of compensatory diuresis then usually followed and lasted for about 20 to 30 minutes.

In all cases of toxaemia of pregnancy this antidiuretic effect of the ultrafiltrate could be demonstrated. The degree of antidiuresis was, however, variable. As in the case of melanophoric response results may be charted under 4 headings: Mild, antidiuresis in 11 cases, 22 per cent; moderate, antidiuresis in 13 cases, 26 per cent; marked, antidiuresis in 26 cases, 52 per cent; absent, antidiuresis in no case, 0 per cent.

It seemed easy to correlate the degree of antidiuresis with hypertension, oliguria, and albuminuria. Out of the 24 patients with hypertension, in 9 the response was "marked", in 10 "moderate", and in 5 "mild". In 2 patients in whom hypertension without oliguria was the notable feature, the antidiuretic response was "mild". It may thus seem reasonable to suppose that the posterior pituitary autacoid is of a complex character, hence hypertension and oliguria may be dissociate phenomena. Of the 26 oliguric patients, in 17 response was "marked", in 3 "moderate", and in 6 "mild". So it will appear that the extent of antidiuretic response follows closely the degree of oliguria present in these patients. If the theory of hyperactivation of the neuro-hypophysis be accepted, such a result is seemingly not very difficult to explain. The antidiuretic autacoid from the posterior pituitary causes oliguria in these patients in as much the same way as in experimental animals. It was, however, an interesting finding that the degree of albuminuria in these patients did not correspond to the intensity of antidiuresis in experimental animals. In 5 patients in whom the albuminuria was severe antidiuretic response was mild. It follows that albuminuria seems to depend not only on the oliguric factor but possibly on a combination of factors, and this contention is supported by physiological experiments. To correlate the action of the ultrafiltrates with known posterior pituitary hormone in these animals, ¼ c.c. of 2½ Voigtlin units of standard pituitary extracts (P. D. & Co.) were injected subcutaneously in the abdomen, and the nature of antidiuretic response studied. The response gathered after injection of pituitrin was found to correspond closely with that obtained with the filtrate. It is of interest to note that a small series of experiments conducted with heart, lung, and kidney preparation also gave identical results relating to the antidiuretic property of the ultrafiltrates.

*Vaso-pressor Effect.*

The third and the most significant biological effect of the ultrafiltrate was found to be on blood-pressure. For these experiments both decerebrated and chloralosed cats were employed. By the usual methods adopted in experimental pharmacology the carotid blood-pressure was recorded on a kymographion. For control the animals were given intravenous saline and normal filtrate in amounts equivalent to toxic filtrate used in the test. The response after toxic filtrate was noted and compared with that obtained from the normal filtrate. It disclosed that with the use of normal saline the blood-pressure compared well with that after normal filtrate, but with toxic filtrate the pressure rose to a considerably higher level. With 8 c.c. of the unconcentrated filtrate or 2 c.c. of the concentrated filtrate (concentration was done by evaporation *in vacuo*) the blood-pressure rose about 15 mm. Hg, depending on the concentration of the pressor element in the filtrate. With saline this rise was always about 2 to 3 mm. Hg, whereas with normal filtrate (same amount) a rise of about 4 mm. Hg was observed. The curve of blood-pressure offers several interesting points for study. These are:

1. *A steep rise.* Within half a minute of the injection the blood-pressure commences to rise and reaches the maximum height during the next half-minute. This indicates that the substance, whatever its nature may be, has a very prompt vaso-pressor action.

2. *A sustained rise and a gradual fall.* The rest of the pressor curve, after the height has been reached, takes a diametrically different course. As the maximal level has been attained the blood-pressure curve, instead of coming down to normal, has been found to maintain its level for about 2 minutes. After this period it started falling, but the decline was very gradual. The normal level was not reached in any case in less than 20 minutes; in 9 instances this period was prolonged to 30 minutes.

3. *Non-responsiveness to repeated injection.* The result of a second injection while the curve was being maintained at a height was studied, and was of profound interest. When such injections were given the blood-pressure not only did not rise any higher, but in some cases showed an actual fall. It is well known in experimental pharmacology that this type of response with vaso-pressor drugs is characteristic of posterior pituitary extracts.

*Results.* The response, as in the two previous instances, may

be classed under 4 headings: Mild, in 9 cases, 18 per cent; moderate, in 19 cases, 38 per cent; marked, in 21 cases, 42 per cent; absent, in 1 case, 2 per cent.

In view of the absence of any previous elaborate work in this line, the gradation was done on arbitrary limits. A rise of 6 to 10 mm. Hg has been reckoned as a mild response, 10 to 15 mm. Hg as moderate, and 15 to 20 mm. Hg above as marked response. It will appear from the details given above that in 80 per cent of the cases of toxaemia of pregnancy the response was moderate or marked. This seemed to be a very interesting observation.

Of the 24 cases associated with hypertension, 21 patients showed marked and the remaining 3 moderate vaso-pressor response with ultrafiltrates. Of the 26 non-hypertensive cases, 16 patients gave moderate and 9 mild response, but in 1 case a vaso-pressor response could not be obtained. This finding seems to be somewhat different from that of Anselmino *et al.*[5] These observers discovered vaso-pressor substance in the ultrafiltrates of patients having a blood-pressure of 180 mm. Hg or above, whereas in the present series the maximal blood-pressure level encountered was 174 mm. Hg in 1 case. In the majority of hypertensive cases in this series the blood-pressure of the patients ranged from 148 to 155 mm. Hg. It is the experience of most obstetricians in Bengal that pregnancy toxaemias are not as a rule associated with a blood-pressure so high as that in other parts of India, namely, Madras, or, for that matter, in other parts of the world. To explain this difference is not the aim in this paper, but this accepted fact can possibly be an explanation for the discrepancy between Anselmino's findings and those of the present observer.

It has not been found difficult to deduce some relation between the antidiuretic, melanophoric and vaso-pressor properties of the filtrate. The results may conveniently be compared at this stage:

| | Melanophoric response, per cent | Antidiuretic response, per cent | Pressor response, per cent |
|---|---|---|---|
| Mild ... ... ... | 14 | 22 | 18 |
| Moderate ... ... ... | 44 | 26 | 38 |
| Marked ... ... ... | 38 | 52 | 42 |
| Absent ... ... ... | 4 | 0 | 2 |

It will appear that a high antidiuretic response is in the majority of cases associated with high vaso-pressor and moderately high melanophoric activity. Again, a low vaso-pressor activity is accompanied by correspondingly low antidiuretic and melanophoric response. This, however, cannot always be axiomated. The type of response obtained with the filtrate is also seen to correspond with the predominating clinical manifestation. For example, in 20 out of 26 oliguric patients marked and moderate antidiuretic property was noticed in the ultrafiltrate, whereas in almost all of the hypertensive cases marked and moderate vaso-pressor response was obtained. Similarly, pure oliguric patients showed comparatively less marked vaso-pressor response, just as the pure hypertensive patients showed correspondingly lessened antidiuretic effect. These results will be more evident from the following tables:

Hypertensive Cases (Total No. 24).

| | Antidiuretic response | Vaso-pressor response |
|---|---|---|
| Mild ... ... ... | 5 | 0 |
| Moderate ... ... | 10 | 3 |
| Marked ... ... | 9 | 21 |
| Absent ... ... | 0 | 0 |

Oliguric Cases (Total No. 26).

| | Antidiuretic response | Vaso-pressor response |
|---|---|---|
| Mild ... ... ... | 6 | 9 |
| Moderate ... ... | 3 | 16 |
| Marked ... ... | 17 | 0 |
| Absent ... ... | 0 | 1 |

The melanophoric activity being limited to the amphibia cannot be compared on the same basis. From the figures stated above it appears the melanophoric response tallies closely with the vaso-pressor response of the filtrate, and this appears to be an expected phenomena.

## Nature of the Ultrafiltrate

The chemical nature of the ultrafiltrate could not be determined with precision. The ultrafiltrate rapidly deteriorated in its potency when treated with alkali or exposed to ultra-violet rays. This seems to be in accordance with Anselmino's observa-

tions. Ultrafiltrates from 10 patients were treated with N/100 sodium hydroxide until the *p*H touched 8. It was found that the extracts subjected to such a degree of alkalinity lost their properties in 20 to 40 minutes. The antidiuretic property was more readily destroyed than the vaso-pressor function. The melanophoric property was the last to disappear. Exposed to Hanovia ultra-violet lamps the filtrate was found to become completely impotent after 7 minutes. The active substance in the filtrate has been found to be fairly thermostable, withstanding a temperature of 95°C. for 20 minutes. It may be mentioned that this peculiar function of the ultrafiltrate compares favourably with that of the posterior pituitary autacoid.

## Discussion

From the above experiments it will appear that the blood of patients suffering from pregnancy toxaemia contains an ultrafiltrable substance which shows on experimental animals:

1. Melanophoric
2. Antidiuretic } properties.
3. Vaso-pressor

Although varying degrees of melanophoric function are possessed by a few chemical substances, like yohimbine, rucine, veratrine, and pilocarpine, it has been proved beyond all doubt by Teague, Noojin, and Geiling[15] that a definite melanophoric response is never obtained by anything other than the posterior pituitary hormone. In untreated individuals the possibility of the appearance of these chemical substances can be completely excluded.

The only substance originating in the human body which causes diminution of the urinary output has been found to be pituitrin, an extract from the posterior lobe of the hypophysis cerebri.[16]

The two substances present in the human circulation known to raise the blood-pressure are the hormones of the adrenal medulla and posterior lobe of the pituitary. The vaso-pressor response of suprarenin (adrenalin) is characteristic and quite unlike that of pituitrin. The kymograph records of the vaso-pressor effect of adrenalin show that the response is of the nature of a quick rise, narrow peak, and a steep fall. The rise of blood-pressure is associated with an accelerated rate of the heart. A second injection, repeated before the action of the first is completely over, always gives a positive response. The kymograph

record of pituitrin shows a rapid rise, sustained curve, and a very gradual fall. The cardiac rate is slightly inhibited due to compensatory mechanism. A second injection, repeated before the action of the first is over, causes a fall (frequently) in the vaso-pressor curve due to diminution of cardiac output.

When all the 3 factors enumerated above are taken together we are left with only one substance to explain the results of the biological experiments, namely, the hormone of the posterior lobe of the pituitary. The melanophore expansion in frogs, anti-diuretic response in guinea-pigs, and the vaso-pressor effect on cats have been found to be due to some substance in the filtrate of toxaemia of pregnancy patients. The filtrates have been tested and found to be protein-free. The possible inorganic substances present in such filtrates cannot be believed to produce this triple response. From the investigations of Cushing and Ählström mentioned above, dealing with functional hyperactivation of the pars posterior hypophysis, it is more rational to believe that the manifestations of toxaemias of pregnancy can be better explained by the assumption of the presence of higher concentration of posterior pituitary secretion in the circulation.

## Biochemical Investigation

Biochemical investigations were chiefly based on the experiments of Urechia, Retezeanu, Groze,[17] and Draper and Hill.[18] The former observers discovered that with experimental injections of pituitary extracts the inorganic phosphate content of the blood rises. The latter observers detected a lowering of the carbon dioxide combining power of the plasma in similar circumstances. In 30 out of 50 patients in the series inorganic phosphorus content of the blood was estimated, while in 25 patients the carbon dioxide combining power of the blood was ascertained. The estimate of the inorganic phosphate content of the blood was made by the method of Youngberg,[19] and the blood calcium by that laid down by Kramer and Tisdall.[20] It is known that calcium and inorganic phosphorus contents of the blood follow a reverse proportion, so to gain a better idea of the inorganic phosphorus metabolism estimation of blood calcium seemed indispensable. The normal inorganic phosphorus level of the blood is 2 to 4 mg. per 100 c.c. and the normal calcium level varies from 9 to 11 mg. per 100 c.c. The inorganic phosphate content in this small series of cases was found to follow closely the intensity of toxaemia. In severe toxaemic

patients the inorganic phosphate level was found to be as high as 8.5 mg., whereas in mild toxaemias it was between 4.5 to 6 mg. per 100 c.c. The calcium content of the blood however showed a much less constant figure, except in one case of severe toxaemia, in which this was 8.4 mg. per 100 c.c., and the blood calcium did not decrease below the normal minimum level. In the majority of cases the blood calcium was found to be 9 mg. per 100 c.c. The corresponding figures obtained from normal pregnant women, however, give sufficient data for comparison. The average content of inorganic phosphorus in the blood of normal pregnant persons was found to be 3.3 mg. per 100 c.c., whereas that of calcium was 11.2 mg. It will thus appear that although the calcium content of the blood did not fall below normal in these toxaemia patients, yet its level was not far beneath the normal average, while the inorganic phosphates showed an unmistakable rise in all these individuals. Authentic literature on the inorganic phosphate level in the blood in toxaemia of pregnancy, is unfortunately not available. The calcium content is also still debatable, and although many observers believe in a low calcium content of the blood in toxaemia patients, the results of investigations of eminent observers like Stander,[21] Minot and Cutler,[22] Davies,[23] and others are not wholly convincing.

Considerable work has been done on the carbon dioxide combining power of the blood in toxaemia of pregnancy. Most observers share a uniform opinion that a state of compensated acidosis exists in toxaemias of pregnancy, and particularly in eclampsia.[24] Dieckmann and Wegner[25] found that the carbon dioxide combining power of the blood was on an average of 51 c.c. per 100 c.c. of the plasma, and the investigations of the present observer corroborate this finding. The degree of acidosis moreover has been found to vary directly with the intensity of toxaemia. In the majority of cases the carbon dioxide combining capacity of blood was found to be 48 to 50 c.c. per 100 c.c. plasma, but in one severe case of toxaemia it was as low as 41 c.c. The average carbon dioxide combining power of the blood in normal pregnant patients was found to be about 60 c.c. per 100 c.c. of blood. The results of the biochemical investigations in toxaemic patients are thus comparable with the experimental observations of Urechia and Retezeanu, Draper and Hill. It thus appears that the toxaemia patients behave in a manner very similar to the experimental individuals who received injections of standard pituitary extracts.

The biochemical investigations thus offer an indirect proof of the presence of hormonic hyperactivity of the posterior pituitary body in persons subject to toxaemia during pregnancy.

## Human Experiments

To tackle the problem from another point of view a small series of human experiments were conducted under the following headings:

1. Effect of the normal pressor hormone of the pituitary on normal pregnant individuals.
2. Effect of pressor hormone of the pituitary on patients suffering from pregnancy toxaemia.
3. Effect of ultrafiltrates obtained from blood of toxaemic patients on normal pregnant individuals.
4. Effect of these ultrafiltrates on toxaemic patients.

### 1. *Effect of the normal pressor hormone of the pituitary on normal pregnant individuals.*

The effect was studied in its action on blood-pressure and urinary output. Pitressin (P. D. & Co.) was employed for this purpose, and $\frac{1}{4}$ c.c. of this drug was given intramuscularly in the deltoid of 15 persons at intervals of 20 minutes until 1 c.c. had been given. The blood-pressure was taken every 15 minutes for 2 hours after the commencement of the experiment. It was found that the vaso-pressor response of normal individuals, with vasopressin, was limited. After the administration of the first dose the blood-pressure rose by about 8 mm. Hg systolic. The subsequent injections were found to be of slight or no effect. In 3 cases of the series a rise of 10 mm. Hg systolic was noticed. The systolic blood-pressure fluctuates, but the diastolic pressure is maintained; 30 to 40 minutes after the last injection, both systolic and diastolic pressures returned to their normal level. The antidiuretic effect of the vasopressin was estimated by the Straus-Greenwald[26] system. The patients were prevented from partaking of any food or drink till the time of investigation, when they were given a pint of water after emptying the bladder completely, then the urinary output was measured hourly for 3 hours. In the normal patient the whole quantity of fluid was excreted during this time. With injections of pitressin it was seen that even normal persons could excrete only 85 per cent of the total fluid intake during the first 3 hours. The anti-

diuresis was noticed to be most marked during the first 1½ hours of the period of investigation.

2. *Effect of pitressin in pregnancy toxaemia patients.*

In contrast with the previous group, this set of patients, 15 in number, presented several interesting features. The vaso-pressor response varied according to the intensity of toxaemia. A prompt rise of blood-pressure was noticed in all toxaemic patients. In patients with mild degrees of toxaemia the increase in blood-pressure was less than in those with marked toxaemic symptoms. A patient with a blood-pressure of 148/128 mm. Hg gave a vaso-pressor response of 22 mm. Hg systolic and 12 mm. diastolic after a single injection of ¼ c.c. pitressin, and this high level was maintained for 8 hours. It is very interesting to note that this patient finally developed eclampsia. The rise in the diastolic pressure was found to be a more constant finding than that of the systolic pressure. Although the systolic blood-pressure was raised in every case after the first injection, it invariably showed different degrees of fluctuation ranging between 5 to 12 mm. Hg. The diastolic pressure was, however, found to be constant throughout the period of experiment and for about 2 hours thereafter. The average rise of systolic pressure in this group of cases was about 18 mm. Hg. The maximal rise observed in one was of 28 mm. 20 minutes after the last injection. Soon after the acme was attained the patient complained of severe headache, giddiness, and nausea, for which sedatives were demanded. It is interesting to record that this patient had a stillbirth 18 days after this experiment. The toxaemia progressed in spite of treatment and after delivery the placenta was found to be masses with infarcts. The rise of diastolic pressure on an average was found to be about 10 mm. Hg. The diastolic rise in all these cases was proportionately higher than the systolic rise. A relation, slight but definite, can be seen between the intensity of toxaemia and the diastolic rise of blood-pressure. The diastolic rise in toxaemia patients was found to be long sustained. The maximal height was maintained for 2 hours after the first injection in all cases, but in one for over 8 hours. The fall of the diastolic pressure as the action of pitressin ceased was also found to be very gradual as compared with the response obtained in normal pregnant individuals. In 4 out of the 15 cases in this series the previous level was never regained (neither systolic nor diastolic) for a period of about one week. In 9 cases about 6 hours elapsed before the previous

level was reasserted. In the remaining 2 cases the former pressure level was regained in 3 hours.

The antidiuretic effect was estimated by the Straus-Greenwald method. It was observed that in 9 of the 15 cases only 60 per cent water clearance was obtained. In 4 cases the clearance was as low as 40 per cent, whereas in two cases only 70 per cent water clearance was noticed during the 3 hours of the experiment. The antidiuretic effect was found to be definitely proportional to the vaso-pressor in these patients. In every case the amount of albumin in the urine increased. In 4 cases in which the water clearance was only 40 per cent, the amount of albumin in the urine more than doubled.

3. *Effect of ultrafiltrate in normal pregnant women.*

This was studied in 10 cases. The amount injected was 5 c.c. given by the intramuscular route. The *p*H of the filtrate had of course to be adjusted before the injection to bring it to neutrality. Sterilization was performed carefully, and in every case the specimen was freshly prepared. (The effect of the injection was first tried on the observer himself.) The nature and intensity of the response obtained with 5 c.c. of the filtrate was found to be almost equivalent to that with $\frac{1}{4}$ c.c. of pitressin, when the filtrate had been obtained from well-marked cases of toxaemia. Both vaso-pressor and antidiuretic effects were of the same type as those with standard vasopressin.

4. *Effect of ultrafiltrate in pregnancy toxaemia patients.*

This was studied in 8 patients in the same manner as in the previous group. The response obtained was of a similar nature. There was a perceptible rise in both systolic and diastolic blood-pressure to a varying degree depending on the intensity of toxaemia. The antidiuretic effect also followed closely that observed with standard vasopressin. The response obtained with 5 c.c. of a filtrate secured from a severely toxic patient was slightly greater than that with $\frac{1}{4}$ c.c. of pitressin (P. D. & Co.). In a patient with advanced toxaemia the rise of blood-pressure was 22 mm. Hg systolic, and 16 mm. Hg diastolic. The water clearance in this case was only 45 per cent. In these 8 cases the study of the inorganic phosphate value of blood was most interesting. In each of the patients there was a remarkable rise in the inorganic phosphorus after the ultrafiltrate was injected. The average rise was nearly 2 mg. per 100 c.c. In the severely

toxic case referred to above the phosphate level before and after injection was 5.5 mg. and 8.5 mg. respectively.

## Conclusion

The anatomical observations of Cushing and Ählström supply morphological evidences of hyperactivation of the neurohypophysis in toxaemias of pregnancy. The biological researches of Anselmino and others pointedly suggested the possibility of such functional hyperactivity. The present series of experiments conducted in 50 unselected cases of pregnancy toxaemia revealed that the blood ultrafiltrates of these patients showed melanophoric, antidiuretic, and vaso-pressor properties. The only substance present in the human circulation known to produce this triple response is the posterior pituitary hormone. Normal pregnant women give very little or no response whatsoever with the ultrafiltrates. It thus appears that there is an increased concentration of the posterior pituitary hormone in the circulation of toxaemic patients. This is corroborated by the biochemical investigation. The rise of the inorganic phosphates and the lowering of carbon dioxide combining power of the blood to the extent met with in toxaemia of pregnancy can be produced experimentally by large and repeated doses of the posterior pituitary extract in normal pregnant women. These facts amply prove that an increased concentration of the posterior pituitary autacoid or functional hyperactivation of the *pars nervosa* of the hypophysis, in all probability, plays a considerable part in the aetiology of toxaemia of pregnancy. The recent work of Browne and Dodds,[27] Kellar,[28] and others also indicates that the commonest residual lesion in toxaemia of pregnancy is essential hypertension, and not chronic nephritis as was formerly believed. Persistence of hyperactivation of the posterior pituitary and chronic vaso-spasm may satisfactorily account for this sequela. But what stimulates this hyperactivation is difficult to explain, and to answer this question there is only a host of theories.

This present small series of human experiments open a new channel of thought. It has been seen that although both normal and toxaemic patients show vaso-pressor and antidiuretic response to injections of vasopressin, yet the reaction in toxaemic subjects is higher and longer sustained than in normal pregnant individuals. The mere presence of a higher concentration of vasopressin does not seem to account sufficiently for this type of reaction. The toxic manifestations produced experimentally in

normal pregnant women required extremely massive doses of vasopressin, whereas with only a small dose of this substance or of the ultrafiltrate worse toxaemic symptoms could be produced in persons already suffering from pregnancy toxaemia. These observations show that the toxaemic patients are in some degree susceptible to posterior pituitary extracts. It has been the experience of many obstetricians that an injudicious injection of pituitrin after the third stage of labour in a pre-eclamptic subject precipitated an eclamptic attack, and often it has been observed that immediately after such an injection the blood-pressure ascended to a dangerous level, quite out of proportion to the amount of pituitrin administered and in spite of the blood-loss attended on the birth of the placenta.

It is difficult to correlate all these facts without assuming not only an existence of a high concentration of the pressor hormone of the pituitary in the circulation, but also a hypersusceptibility of these patients to this hormone. From clinical experience we know of similar idiosyncrasy to other natural hormones of the body, namely adrenalin and insulin. At the present stage, while it is difficult to prove absolutely the existence of the supposed hypersusceptibility of the pregnancy toxaemia patients to the increased content of the posterior pituitary hormone in the blood, further experiments and investigations may supply more data to enable us to reach that conclusion.

## Summary

1. Anatomical and experimental observations relating to functional hyperactivity of the posterior pituitary in the aetiology of pregnancy toxaemia are briefly narrated.

2. Experimental observations with blood ultrafiltrates of 50 unselected cases of toxaemia of pregnancy are related with respect to their melanophoric, antidiuretic, and vaso-pressor responses in animals.

3. Results of biochemical investigations carried out with a view to determine calcium and inorganic phosphate content, and the carbon dioxide combining power of the blood are mentioned.

4. Experimental and biochemical investigations conducted suggested a functional hyperactivity of the posterior lobe of the pituitary body in toxaemic states associated with pregnancy.

5. The effect of standard posterior pituitary extract and sterilized ultrafiltrate was studied on a small series of human experiments on normal and toxaemic patients.

6. The theory of hyperactivation of the neuro-hypophysis in toxaemias of pregnancy is supported.

7. The possibility of hypersusceptibility of the toxaemia patients to the posterior pituitary autacoid is suggested.


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# The Suture of the Perineum using Local Anaesthesia

BY

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IN recent years the care of the perineum and its repair in the case of injury in labour has received well-merited attention. The great importance of early suture has been emphasized, and numerous authors have laid stress on the necessity of careful co-aptation of the tissues in anatomical layers, the operation to be carried out as soon as possible after labour. Some even recommend that it should be done before delivery of the placenta. Certainly if the latter takes an hour or more to separate, suturing is something to occupy the time, but there are many more cogent reasons why it is unwise to do it then. For example, attention may be diverted from the control of the uterus and post-partum haemorrhage ensue. De Lee[1] mentions a case in which the patient died from post-partum haemorrhage because the uterus was neglected in order to carry out perineal repair before delivery of the placenta. Again, a manual removal of the placenta may on rare occasions become necessary, and the carefully repaired perineum may not only suffer, but be a real hindrance to the performance of the operation.

The technical details of the actual suture have received very adequate attention, and every modern standard textbook has space devoted to the subject. What has received much less notice, however, is the way to make the operation painless. Too often stitches are inserted without any anæsthetic at all, and this in a region of the body as sensitive as the finger-tips. While it is admitted that the bruising and tearing of the tissues has a numbing effect on them (this will be referred to again later) yet the application of even one skin stitch can cause considerable pain, and to attempt anything further would be impossible. The patient may still be analgesic from drugs given to control the pain in labour, but even so, the sharp stimulus of a needle may prove very unpleasant for her.

When general anaesthesia has been used in the labour, the position is different. Obstetric operations such as delivery by

the forceps and version require full anaesthesia, and in these cases the perineum may be sutured under the same anaesthetic as that given for the operation, providing that the placenta comes away early, and the anaesthesia is not prolonged unduly. The new gas and air method is satisfactory for labour, but in the author's experience eminently unsatisfactory for the suture of the perineum. For one thing, the analgesia obtained is relatively slight; but what is more important is that the patient gets very restless and it is impossible to make a fine and careful repair. Older fashioned methods such as chloroform drops for labour suffer again from the fact that they do not produce anaesthesia either deep or lengthy enough to permit the operation of suture.

Finally there is a large series of cases in which an anaesthetic has not been used for the labour, and these call for some pain-relieving method if a tear has to be repaired.

Suture of the perineum, it has already been pointed out, is an operation which must be done with care. It is not just a case of putting in a stitch in the half light with the patient jumping off the bed. It means sometimes a long operation if care is really taken to suture the wound correctly, and the patient should be quiet and resting, in a satisfactory position, in a good light, and every aseptic precaution must be taken.

To fulfil all these conditions the only method apparently available is to administer to the patient a full general anaesthetic. If one has already been given for an obstetric operation, then it may be prolonged (but not too long, as mentioned above) to permit the repair. What of the other cases? One is at once faced with the necessity of obtaining an anaesthetist (this may be no easy matter in these times) and asking him to give a full general anaesthetic to a woman who has just been through a strenuous ordeal, who has lost a certain amount of blood, perhaps a lot, and whose condition is probably one of partial exhaustion. If the surgical patient be compared with the obstetrical, it is remembered that before a patient has an operation with a full general anaesthetic, the utmost care is taken to ensure that he or she arrives in the theatre for the administration in the best possible condition. Yet no one could say that the woman after the exhausting strain of labour is in a condition comparable to that of the surgical case. In spite of all these obvious facts, obstetricians continue light-heartedly to take the responsibility of administering general anaesthetics to women exhausted after labour.

Consideration of all these points led to a search for an alter-

native method. Most of the standard textbooks on obstetric operations give very little help. If any mention is made at all it is merely that "the patient should be anaesthetized." However, De Lee goes so far as to say that local anæsthesia is a practical possibility and he strongly recommends it. In the description of his technique, however, he does not make it clear if he means local infiltration, or paravertebral block in the sacral region. Eden and Holland[2] state that for certain types of case local infiltration anaesthesia is suitable, while Mudalier[3] advocates its use, with the reservation that for severe tears it is not so satisfactory. In the literature Way[4] wrote a short memorandum on the method, based on experience in a London Maternity Hospital, and strongly advocated the adoption of this technique, stressing its advantages both from the patient's and the surgeon's point of view. Walther[5] endorses these points.

Accordingly it was decided to try the method of local infiltration, and after using it with success on a number of patients both in the wards at Charing Cross Hospital, and (what is more important) in the houses of district cases, it was felt this method was of the greatest value, deserving of far more common use, and which in all but a few cases (those receiving a general anaesthetic for other reasons) could, and indeed should, be used to the exclusion of other methods.

*Technique.*

For the reasons stated previously, the operation is never undertaken until the patient is delivered of the placenta. When this occurs a sterile pad is placed over the vulva, and ergometrine or pituitrin given if necessary. The patient is then cleaned, made comfortable, given a warm drink and food if she feels like it (a valuable restorative, but one impossible prior to general anaesthesia), and fresh clean linen is placed on the bed. It is remarkable what a change these simple proceedings produce in a patient, especially when the apprehension of a general anaesthetic is not present.

While these preparations are going on the necessary fresh surgical instruments are laid out, and the surgeon scrubs his hands again, changes his gown, and puts on fresh rubber gloves. The patient is then placed in the lithotomy position, with her head on a pillow if she likes. Sterile towels are next placed over her, and the vulva washed down with dettol solution* (poured

* This must be a weak solution (1 drachm of pure dettol to 1 pint of water) otherwise there may be a serious risk of burns.

on, not swabbed). The sterile towels should be arranged to exclude the anus as far as possible.

Too much emphasis cannot be laid on the aseptic precautions detailed above. Often one sees carelessness—the surgeon not changing his rubber gloves, or fresh instruments and towels not being used. It is admitted that outside a hospital all the facilities may not be available, but even so, there is no excuse for ignoring simpler points.

No other antiseptic is used on the skin; the surgeon then seats himself in front of the patient, and a portable light is adjusted to give optimal illumination.

Very often a little ooze from the uterus at this stage obscures the rupture. The perineum is gently swabbed (from before backwards, not using the same swab twice) and very gently (remembering the patient is feeling all this) a swab soaked in the dettol solution is pushed up the vagina as far as the upper end of the tear. This stops blood from trickling out. It may be objected that such a procedure is likely to introduce infection, but in the author's experience harm has never come of it, for the trickling blood has to be wiped away in any case, and suture materials and instruments passed just as far up the vagina. Indeed a large moist swab may even be of advantage in keeping out infection during the operation.

A large syringe (not less than 20 c.c.) is then filled with novocaine 2 per cent. The novocaine must be taken from freshly opened ampoules, and not from rubber capped or ordinary bottles, since the risk of contamination is too great. A fairly long needle of medium bore is used.

It may here be remarked that adrenaline combined with novocaine was not used, as it was felt that the effects of the former on blood-pressure and the heart might cause difficulty. Actually the slight diffusion of the solution that takes place is really an advantage as it helps to spread the field of anaesthesia.*

A careful examination is next made to ascertain the extent of the tear. If done carefully this need not hurt the patient, but if the parts are very tender, this careful examination must be postponed until the injection is partly done. Here it may be remarked that a tear should never be dismissed light-heartedly as "just a snip." Without examination it is impossible to be cer-

* Recently the author has used in other surgical fields a solution of percaine (1 in 1000) combined with adrenaline. This has proved in every way superior to novocaine, and it is felt that it would be equally suitable for perineal suture.

tain of the extent of a tear, and very often what appears at first glance to be a superficial nick in the perineum or fourchette actually extends up the vagina, and often deeply too. These apparently trivial tears are nearly always found to be more extensive than at first sight appears.

If care is taken in the injection the patient will probably feel nothing: at the most she will only feel two pricks. The solution must never be injected into the undamaged skin, but only from a torn surface outwards underneath the skin. Accordingly the first injection is made at the posterior end of the tear starting on one or other side. The needle is run outwards under the skin from the side of the tear. It should be as superficial as possible and, as the injection is made, the skin should be seen to whiten. The needle is then pulled out slightly, and then returned much deeper, so that the novocaine is now put deep in the perineal body. Withdrawing the needle somewhat again, it is now directed forwards, almost parallel with the cut surface, and infiltration made into the area forward of the first injection point. The needle is now completely withdrawn, and a new injection made into the torn surface ½-inch to ¾-inch in front of the first point, the same three movements being repeated. This is continued until the upper end of the tear is reached (usually high up the vagina) and then the opposite side of the tear dealt with in the same way. It is clear that the third movement of forward injection infiltrates the area immediately in front, and the needle goes in next time through an already anaesthetized area, and the patient does not feel any prick.

It is important to see that the superficial part of the injection is only just underneath the skin or mucous membrane of the vagina, otherwise the patient will feel the suturing needles which are passed in through it.

When the whole tear has been infiltrated it is again carefully swabbed and explored, and then the suturing commenced. It is unwise to ask the patient if she can feel anything; this may arouse suspicion in her mind that the operator is dubious about his anaesthesia, and she may in apprehension say "Yes" in order to put off the moment of starting the actual stitching. In this part of the body, as elsewhere, when using spinal or local anaesthetics, the surgeon must convince the patient of the infallibility of his technique, because if he does not, the patient may become very difficult—always anticipating that the next move will cause her pain. If the injection is done with care, and the method described above carefully followed, the obstetrician may

be confident of success. In any case a gentle preliminary test with a pair of pressure forceps on the supposedly insensitive skin is sufficient.

In general the amount of novocaine used varied from 20 to 40 c.c., with an average of 30 c.c. These amounts are considerably in excess of those specified by Way in his article. It was found that less amounts were required when the operation was performed immediately. One or two patients did not have immediate suture for various reasons, and it was found that the longer the time allowed to elapse the more the solution needed. This is presumably because the bruising and numbing of the tissues produced by the trauma of labour had begun to wear off. On the other hand the operation was often found to be easier in these cases, because bleeding had stopped, and the tissues were less oedematous. Generally speaking, however, when there was delay, complete anaesthesia was more difficult to achieve, although no case was left more than 18 hours.

Before starting the actual stitching it is a good plan to place a sterile gauze swab over the tear and to exert gentle pressure for a few moments. This is not so much to give the novocaine time to take effect, as to allow the swelling of the infiltrated tissues to subside somewhat.

The repair is on the lines usually described. Deep interrupted catgut stitches are placed in the perineal body and superficial perineal muscles (particularly in the external sphincter ani if torn), these are followed by a continuous superficial catgut stitch along the posterior vaginal wall. Silk-worm gut stitches inserted deeply are put through the perineal skin. If their insertion causes discomfort, they may be inserted painlessly from the cut edges outwards and upwards through the skin. This involves threading the needle on each end of the suture, but the slight extra trouble is well worth while. In the series of cases below, healing was found to be so good that it often extended forwards some distance in front of the most anterior suture; great care must, therefore, be taken not to stitch the perineal skin too far forwards, as otherwise the introitus will become narrowed. The silk-worm gut stitches in the perineum are left long and all tied together; this was found best for the patient's comfort as she did not sit on the short sharp ends which are otherwise left. The vulva is now swabbed with the dettol solution, care being taken to remove the swab from the vagina.

Only a sterile pad over the vulva is used for dressing, and changed three times a day. The toilet of the perineum, including

the routine regular swabbing and after the use of the bed-pan, is carefully carried out, dettol solution being once again the antiseptic of choice. The parts must be carefully dried each time.

Silk-worm stitches are removed on the 10th day. In the series of cases given below on two occasions a gauze roll was placed over the perineal wound and held in place by tied over sutures. This was soon abandoned, however, as the gauze roll could not be kept dry, and the skin became sodden and uncomfortable. Even so, infection did not occur.

A series of cases which occurred in the wards or district of Charing Cross Hospital, London, is given below. First and

TABLE OF A SERIES OF CASES

| Name | Age | Parity | Weight of baby | Type of tear | Time of suture | C.c. novocaine used |
|---|---|---|---|---|---|---|
| D.B. | 24 | P | 6 lb. 5 oz. | Slight first degree | Immediate | 8 c.c. |
| L.P.* | 32 | M | 6 lb. 8 oz. | First degree | Immediate | 10 c.c. |
| M.S. | 27 | P | 6 lb. 8 oz. | First degree | Immediate | 12 c.c. |
| E.W. | 27 | P | 7 lb. 6 oz. | First degree (minor) | Immediate | 5 c.c. |
| P.H. | 28 | P | 6 lb. 11 oz. | First degree | 10 hrs. later | 16 c.c. |
| F.E.* | 32 | M | 8 lb. 4 oz. | 1st degree involving posterior vaginal wall | Immediate | 15 c.c. |
| D.B. | 26 | P | 6 lb. 6 oz. | Full 2nd degree | Immediate | 25 c.c. |
| E.A. | 21 | P | 8 lb. 8 oz. | 2nd degree | Immediate | 30 c.c. |
| C.B. | 27 | P | 8 lb. 8 oz. | 2nd degree | 18 hrs. later | 38 c.c. |
| L.C. | 24 | M | 8 lb. 10 oz. | Severe 2nd degree through old scar of previous repair | Immediate | 25 c.c. |
| W.G. | 21 | P | 9 lb. 6 oz. | Severe 2nd degree involving anal sphincter | Immediate | 25 c.c. |
| B.M.* | 24 | P | 6 lb. 10 oz. | Full 2nd degree | Immediate | 25 c.c. |
| L.S. | 26 | P | 7 lb. | Advanced 2nd degree tear involving anal sphincter | Immediate | 30 c.c. |
| A.S. | 24 | P | 6 lb. 6 oz. | 2nd degree | Immediate | 20 c.c. |
| N.T. | 29 | P | 8 lb. 6 oz. | 2nd degree | Immediate | 25 c.c. |
| J.W. | 19 | P | 6 lb. 11 oz. | 2nd degree | Immediate | 30 c.c. |
| P.M. | 32 | P | 7 lb. 2 oz. | Advanced 2nd degree | Immediate | 32 c.c. |

Result: Healing by first intention in all cases.

* District case.

second degree tears are represented, in all grades from a slight nick of the fourchette to one that nearly tore through the anal sphincter. In all of these the healing was complete when the stitches were removed, there were no cases of pyrexia following the operation, and in no case did any infection, superficial or deep, appear. All cases were re-examined in 6 weeks, and all showed a satisfactory perineum. In no case was complaint made of a tender scar.

Owing to selective admission most of the cases occurred in primiparae. In one multipara a rupture took place through an old badly repaired tear, but healing was satisfactory after re-suture with local anaesthesia.

The above series of 17 cases is entirely unselected and comprises the entire number dealt with in a period of about 4 months, with the exception of those patients in whom the repair was made under general anaesthesia continued from an obstetric operation. The term "healing by first intention" implies that when the sutures were removed, skin and deeper structures were firmly united, and there was no evidence of sepsis in the scar. In many cases the skin around the points of entry and exit of the stitches was slightly moist, but this always cleared up in a day or so, and could not be regarded as infection of the wound.

## Summary

1. An outline is given of possible methods of anaesthesia useful for the performance of the operation of perineal suture after labour.

2. Emphasis is laid on the importance of careful technique in the operation.

3. The serious disadvantages of general anaesthesia administered after a labour are pointed out, and comparison is drawn between the obstetrical and surgical patient.

4. Local anaesthesia is suggested and its advantages discussed.

5. The technique of the operation, using local anaesthesia, is described. Particular attention is paid to the adequate regard of asepsis, to the correct method of infiltration, and to the necessity of careful examination of all tears and suspected tears. Attention is also drawn to the optimal time for performing the operation as indicated by the amount of novocaine used in relation to the anaesthesia produced. A few notes are added about the method of suturing used in the cases under review.

6. The after treatment is described.

7. A small series of cases operated on by the author is given, and the satisfactory results noted. All these cases were of in-patients or out-patients of the Maternity Department, Charing Cross Hospital, London.

## Conclusion

A method has been described of suturing the perineum after rupture in labour, using local anaesthesia (2 per cent novocaine). The obvious advantages and satisfactory results would seem to recommend a more widespread adoption of the technique.

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I should like to acknowledge my indebtedness to Mr. Arthur Gray, Senior Obstetric Surgeon to Charing Cross Hospital, for his kindness in allowing me to use the method on patients under his care, and to quote from notes on his cases for the purposes of this article.

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# Hyperemesis Gravidarum, and High Vitamin Therapy

BY

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MANY investigators have searched for some elusive hormone or altered product of metabolism, the correction of which would cure hyperemesis gravidarum. However, dramatic clues of this nature have not been forthcoming. As a result, one would be led to believe that the cause of the condition can be rationalized along purely physiological lines. On the other hand, there is strong presumptive evidence that some patients suffering from hyperemesis gravidarum have died, not from that disease, but from unsuspected damage caused by avitaminosis. In other words, although the vomiting was alleviated, the probable avitaminosis was not recognized and itself did not receive any treatment, thereby leading to a fatal issue. The effort of this article will be to review the situation up to the present, and to attempt to establish the need for high vitamin therapy in this complication of pregnancy. The pathology of Wernicke's encephalopathy will be introduced as proof that in advanced hyperemesis gravidarum, changes do take place that hitherto have not been recognized, and were, therefore, excluded from previous plans of treatment.

Nausea and vomiting for several weeks in early pregnancy is so common as to appear almost physiological. However, when this interferes materially with fluid balance, acid-base equilibrium or other phase of nutrition, it must be classed as abnormal and dangerous. Such is hyperemesis gravidarum, and it is this form of pregnancy-vomiting with which this paper is concerned. As a cause of this condition the reflex theory has been discarded as unsound. The toxaemic and carbohydrate deficiency theories have been renounced as prime causes. The endocrine theory is likewise losing colour from lack of effective argument or application.[1, 2, 3] This leaves as an initial cause the neurosis theory recently revised by Atlee.[4] Atlee holds that psychological conflict is present. The unconscious mind makes a distorted attempt to get rid of the embryo, and vomiting ensues, even in spite of the conscious desire for

a child by the patient. This, however, does not explain hyperemesis in women who do not know they are pregnant.

Nevertheless, supporters of this last theory suggest that in the presence of a basic neurotic element, the vomiting is perversely welcomed because the patient either enjoys the attentions she receives while ill, or achieves psychological 'escape' from domestic tribulations. The vomiting is thus voluntarily continued to the point at which it gets beyond her control. In the process, electrolytes, carbohydrates, and fluids are robbed from the body, while at the same time the patient suffers from lack of intake of vital food elements. Depletion of liver glycogen follows and acidosis from abnormal fat metabolism results. The glycogen inadequacy leads to injury of the liver, so that metabolic products are not properly detoxicated. Concomitant constipation and dehydration lead to faulty elimination, and the eventual outcome is retention of metabolites in the blood-stream producing a toxaemia. The toxaemia and acidosis further aggravate the vomiting and a vicious circle is established. Here the literature mentions the subsequent deleterious effect on the various organs and tends to drop the subject, making very little reference to the consideration that at the same time avitaminosis may be inflicting serious super-added harm.

Recent views on the pathology of hyperemesis gravidarum are well illustrated in a paper by Sheehan.[5] His personal investigations and literature references throw a new light on the subject. He believes that the central necrosis of liver lobules so frequently described is due to delayed chloroform poisoning (as in anaesthetics given for therapeutic abortion), and that cloudy swelling of the kidney parenchyma is due to post-mortem autolysis. In his series of cases, the first consistent finding was that the heart was atrophied, and that the severity of this change was proportionate to the duration of the vomiting. Possibly the hyperemesis exercised some trophic action on the heart, but there was not any histological proof of the occurrence of a toxic myocarditis. The liver sometimes showed fatty infiltration, usually centrilobular. He suggests that this was due to mobilization of body fat consequent upon starvation. The kidneys showed fat in the first convoluted tubules in only those cases which received glucose therapy *per rectum*, but not in those cases which received adequate intravenous glucose. This is of interest, as the renal fatty change is probably due to ketosis which is, apparently, best treated by glucose administered into the blood-stream. The pathological lesions in these patients, therefore,

were in his opinion the results of vomiting and lack of food. Further than this the two cases of hyperemesis which were investigated by post-mortem examination since he started examining the brain for the histo-pathological appearance of Wernicke's encephalopathy, showed that disease. This pathology also occurred in the brain of a case of ideopathic vomiting of late pregnancy. Wernicke's encephalopathy is a pathological entity, exhibiting vascular and tissue changes in certain selective sites in the brain, notably the corpora mamillaria, and walls of the third ventricle and aqueduct. For greater details of this pathology, the reader is referred to references 6 and 7.

The cause of Wernicke's encephalopathy is probably avitaminosis and is rationalized as follows. The first established cases were described in deaths following Korsakow's psychosis, and were attributed to chronic alcoholism. However, it is remarkably consistent that a large number of these cases were associated with gastro-intestinal disturbance, chronic gastritis, vomiting and polyneuritis (a picture like that of advanced hyperemesis). Neuburger[6] suggests three factors acting either singly or in co-operation, as the responsible causes. They are, an endogenous toxin or toxins, anaemia, and a vitamin deficiency. He argues that in the abnormally functioning gut, an endogenous toxin is formed which escapes detoxication by a damaged liver (evidenced by fatty degeneration) and produces the encephalopathy. This has not been convincing. Campbell and Biggart[7] claim vitamin $B_1$ deficiency as the cause on the following basis. In alcoholic polyneuritis the victims have a vitamin $B_1$ intake below minimal requirements, and the polyneuritis is relieved by vitamin $B_1$ administration. In vomiting of pregnancy there is present: (*a*) Poor food intake (deficient vitamins). (*b*) Rise in metabolic rate (requires more vitamin $B_1$ than usual). (*c*) Treatment of hyperemesis with carbohydrate (this increases the demand for vitamin $B_1$). (*d*) Gastric hypofunction (impaired vitamin absorption). (*e*) Pregnancy itself requires extra vitamin $B_1$.

Therefore, presumptive evidence would suggest that $B_1$ deficiency was the casual factor. However $B_1$ avitaminosis (beri-beri) does not show Wernicke's syndrome at autopsy, and the authors suggest that their $B_1$-deficiency theory is linked with some other factor. This is probably the case. Peters[8] points out that in the brains of $B_1$-deficient pigeons, carbohydrate metabolism is incomplete. As a result, pyruvic acid accumulates, in consequence of which the tissues lose their power to take

a child by the patient. This, however, does not explain hyperemesis in women who do not know they are pregnant.

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up oxygen, and the subsequent decrease in tissue respiration leads to tissue damage in the brain (and also kidneys and muscles). It is possible that the same abnormal metabolic conditions in a $B_1$-deficient human brain may predispose certain areas, i.e., corpora mamillaria, to the action of a super-added toxin (as of Neuburger), or a super-added deficiency of another vitamin, and thereby produce Wernicke's encephalopathy. Here, for reason of strengthening my argument in the next two paragraphs, I wish to mention the symptoms usually attributed to Wernicke's encephalopathy. In brief, the clinical picture of Wernicke's encephalopathy is described as one of drowsiness, confusion, apathy, dullness, and loss of memory, terminating in coma. Sometimes there is loquacity, and eye signs such as squint, diplopia, or retinal haemorrhages. Less frequently huskiness of the voice and occasionally Korsakow's psychosis or polyneuritis develop.

In a further perusal of the literature, Kurzrok's[9] book on "Endocrinology" would indicate that hyperemesis gravidarum is very similar to the clinical picture of Addison's disease except for the absence of pigmentation. Kemp,[2] in an article, points out that the symptoms of adrenal cortex insufficiency are first anorexia and listlessness. Then follow morning sickness, blood-pressure diminution as sodium and fluid loss occurs, impaired renal function and disturbed carbohydrate metabolism with depleted liver-glycogen. He adds that in pregnancy the adrenal cortex hypertrophies to meet the increased demand for cortin, and that adrenal cortical hormone deficiency may be the cause of excessive vomiting, as sufficient adrenal hypertrophy may not occur until the 3rd month.

On the strength of Kemp's statement, Freeman and Melick[10] used adrenal cortical extract in 1935 to treat an unresponsive case of hyperemesis gravidarum. They were so pleased with the results that it was decided to treat similarly all cases of pregnancy-vomiting that came under their care. In 1937 they, with McClusky[3], published the results of treatment of 78 patients. They were still delighted with their results. Their conclusions, however, are not impressive because the mild or first two groups (47 of the 78 cases) were not very severe, as the patients did not show any ketosis. Each patient was cured on 100 cortical tablets in 1 to 2 weeks. Against this, 15 people in the 3rd group with severe nausea and vomiting, marked weakness and slight ketosis, were cured in 1 to 5 days by hypodermic injection of Armour's adrenal cortical extract 1 ampoule t.i.d. × 3

days or until cured. These latter quick responses may have been due to the psychological effect of the needle. Besides, in the stubborn cases the patients were isolated, and intravenous glucose 1,000 c.c. b.i.d. with insulin were injected. This publication is mentioned because in their 4th group labelled "pernicious vomiting" 15 of the 16 patients were cured in 3 to 5 days on the cortical extract, but in one case the patient failed to respond. This case proceeded with increasing severity until, to quote: "her mind began to wander . . . difficulty in concentration . . . slow answering of questions." Then "she became irrational . . . lost her memory . . . at times did not recognize her husband and her children. She was profoundly weak . . . and developed a peripheral polyneuritis"; at this late point vitamin concentrates were given by hypodermic injection plus such as would be retained by mouth. The patient immediately showed improvement, and from then on recovered uneventfully. This is truly a clinical picture of Wernicke's encephalopathy, although not described as such. The keystone in its cure was the administration of vitamins. The experiment *de facto* is more valuable in that the disease was treated by what might virtually be called trial and error methods, and of those used, vitamins most remarkably succeeded.

It is difficult to indicate the various manifestations of a lack of the different vitamins in hyperemesis gravidarum, but every clinician is aware that severe clinical pictures are produced when these essentials to life are absent. We have already dealt with the probable effect of a lack of vitamin $B_1$. $B_2$ deficiency causes nervous and gastro-intestinal symptoms which will be hard to assess in this disease. The bleeding spongy gums, haematuria and muscular periosteal pain sometimes seen may be evidence of scurvy, or C-avitaminosis. At this point it may be stressed that in a condition in which so little is known of the exact aetiology, it would be foolish to imply that vitamin therapy will guarantee a cure. What it is desirable to emphasize is, that when vomiting has been long continued, avitaminosis in some degree will probably be present. Hence, whatever else is tried, it should be assured that avitaminosis will not be allowed to develop during the course of treatment.

If one institutes one's principle of treatment on such facts and essential pathology as have been established, a really rational course results. In hyperemesis gravidarum the treatment must be instituted early, conscientiously, and with such wisdom as our present knowledge permits, remembering that

early control of vomiting will allay the concurrent atrophy of the heart. A complete physical and neurological examination should precede all therapy, in order to rule out symptomatic vomiting. The elimination of the neurotic factor comes next, and treatment should be as directed towards a hyper-irritable nervous system and disturbed psyche. Suggestion, isolation from friends, relatives, and over-solicitous attendants, together with the adjustment of contributory mental factors, i.e., problems concerning husband and family, are most valuable. Sedatives are given in sufficient quantity to stem the vomiting, quieten the nervous system (bromides, phenol-barbital, and pento-barbital are satisfactory on rectal administration), and ensure sleep.

Another vital problem is dehydration. With this, the question of hepatitis and ketosis arises, from both of which the patient is protected by glucose. The patient is not allowed anything orally except mouth-wash. Continuous intravenous 5 per cent and 10 per cent glucose in normal saline alternating every 1,000 c.c. should be given (because as previously pointed out, fatty change in the kidneys occurred only when rectal glucose was administered). There is no need to insert a cannula into the vein by a cut-down method; a number 18 (wire gauge) needle introduced directly into that vein running along the ventro-lateral aspect of the forearm is sufficient. When strapped to the skin this allows the patient sufficient movement to change into a more comfortable position from time to time, and will function up to 5 days continuously. Regulated at 15 drops a minute, about 3,000 c.c. of fluid are run in during 24 hours. This quantity will not overburden the heart. Ten c.c. of 10 per cent calcium gluconate added to each litre of fluid further protect the liver. Twelve units of soluble insulin given in each litre of glucose-saline ensure utilization of the glucose and glycogen formation.

In solving the problem of avitaminosis, even though the patient is vomiting, vitamins $B_1$ (aneurin), $B_2$ (nicotinic acid), C (ascorbic acid), and A and D as Dekadexolin (Glaxo Ltd.) can all be given by intramuscular injection. If the patient can retain articles by mouth, capsules containing most of the known vitamins, in good concentration, are obtainable from reliable drug houses.

In desperate cases starvation can be mitigated by a small duodenal tube. Passed through the nose and strapped to the face, the tube permits the drip feeding of fluid foods (such as milk, eggs, syrup, fruit juices and vitamin preparations). This often

produces remarkable results in spite of severe vomiting. With regard to diet, the strain on the liver and kidneys can be eased by limiting the ingestion of proteins. A reduced intake of fats will diminish tendencies to acidosis. These two points dovetail with questions of elimination, and would not be complete unless precautions against the inevitable constipation were taken by enemata. After the vomiting has ceased, and the urine is free from acetone, the diet can be progressively increased, beginning with easily digested foods.

Signs of favourable response to treatment are: the cessation of vomiting (fallacious especially if Wernicke's encephalopathy has developed), an increasing output of urine and height of blood-pressure, a slowing regular pulse-rate of good volume, normal temperature, absence of jaundice and albuminuria, a clean moist tongue and a clear and alert psyche. Evidence of unresponsive or progressive disease is: no improvement after at least 48 hours of intensive treatment. Bandstrupp[11] states that any one of the following signs is sufficient justification for the termination of pregnancy: Jaundice or bile in the urine, persistent albuminuria, a pulse or temperature rise to persistently over 100, a persistently low or falling blood-pressure, or the appearance of retinitis. To this latter list may be added mental or nervous changes. Once these signs appear time must not be lost in evacuating the uterus completely. The preferable methods are abdominal hysterectomy with local anaesthesia, vaginal hysterotomy or cervical dilatation and uterine curettage with sacral block. It is interesting, however, to note that Reed and Teel[12] (who report 91 cases of hyperemesis gravidarum out of 14,600 deliveries) had such a high mortality with therapeutic abortion after the above symptoms were reached, that they decided upon much the same conservative therapy as outlined here. Since good results were obtained and deaths did not occur on conservative treatment in their severely advanced cases (two patients with severe polyneuritis), they now consider therapeutic abortion in this advanced stage contra-indicated. The author had a patient with all the indications for termination of pregnancy present plus advanced emaciation, but as the patient refused the offer of pregnancy termination, the routine outlined here was followed, and after a short stormy spell, the patient recovered uneventfully. Nevertheless, to stand by in the face of such symptoms and not terminate pregnancy requires extremely strong convictions, and is a responsibility which conscientious obstetricians to-day would be reluctant to

accept. However, even if the pregnancy is terminated, the vitamin therapy should continue.

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# Ante-Partum Haemorrhage with Retention of Dead Foetus

BY

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THE case recorded here is of interest both on account of the unusually long period over which the dead foetus was retained in the uterus, and also as illustrating some of the difficulties encountered in the diagnosis and treatment of native patients under island conditions.

The patient was a full-blooded Solomon Island woman, about 30 years of age. She was first seen at the antenatal clinic at the hospital in June 1938, when she was about 24 weeks pregnant. She gave a history of 6 previous pregnancies, of which the first 5 ended in normal labour, and the 6th in a death *in utero* with spontaneous delivery. Only two of the five children survive. Examination at this time did not reveal any abnormality: foetal movements were present, but the heart was not heard; blood-pressure was 115/70. She was told to report in 2 months, and returned to her own village on another island, some 15 miles' canoe-journey distant from the hospital.

The patient did not report at the appointed time, and I next saw her on October 24th, when I visited her village at the beginning of a circuit of the island of Ranono. She had been ill for 24 hours, complaining of severe abdominal pain and vomiting; there was no history of vaginal bleeding. On examination she appeared moderately collapsed, with rapid pulse and profuse sweating. She was so restless and so intolerant of examination that I suspected an hysterical element in her symptoms, especially as there was a history of a recent domestic quarrel. The abdomen was tense and tender, distended, and could not be palpated satisfactorily: the uterus did not appear to be contracting, and the foetal heart was audible with difficulty. The spleen reached half-way to the umbilicus, and was tender. My journey round the island had to be completed to scheduled

time, so I administered a sedative and promised to return in 2 days.

On October 26th I again examined the patient in her village. The pain had not ceased in the interval. There had been a moderate vaginal haemorrhage after we left on the 24th, and another early that morning. There was little change in the patient's general condition, but the foetal heart was no longer audible. I transferred her to the launch and returned to Bilau. Vaginal examination on arrival revealed a soft cervix with no sign of dilatation, and a very slight oozing of dark blood. The temperature was 101°F.; pulse-rate, 120; red cells, 1,500,000 per c.mm., and haemoglobin, 30 (Sahli).

Unfortunately I had been home only half an hour when a call came to go to visit a patient in the Marovo Lagoon, some 150 miles away, in circumstances which left me no alternative but to depart immediately. The patient was, therefore, left in the care of my nursing staff (two fully qualified nurses), who had instructions to give pituitrin and expedite delivery should further severe bleeding occur. I returned on October 30th. The patient was still febrile, but the general condition had improved—pain less, abdomen softer, and no further bleeding. The patient remained febrile, but gradually improving for another 3 weeks, at the end of which she was completely symptom-free. and remained so for 4 weeks. Pain, fever, and purulent vaginal discharge then returned, and led to a long illness, which was terminated only by evacuation of the uterus by vaginal hysterotomy 22 weeks after the onset of symptoms. The progress of the case is shown in the following extracts from the notes:

November 2nd. Red cells, 1,800,000. Haemoglobin, 50 (Sahli). Liver extract, 2 c.c. on alternate days.

November 6th. Red cells, 2,180,000. Haemoglobin, 45 (Sahli). White cells, 10,400. No parasites seen in blood film. Blood transfusion, 15 ounces on November 6th.

November 10th. Red cells, 2,800,000. Haemoglobin, 68 (Sahli). Feeling better.

November 14th. Attempted medical induction by quinine and castor oil technique. No results.

November 18th. Second attempt at medical induction also unsuccessful.

November 29th. Temperature completely settled. Slight abdominal tenderness; uterus unchanged in size, and foetal parts can be palpated, but indistinctly.

December 8th. No pain or pyrexia. The patient was very

anxious to go out, and refused to consider any surgical interference at this stage, though warned of the certainty of future complications. She was discharged to the out-patient department, and given 8 daily injections of theelin, without result.

January 9th. Re-examined at out-patient department. Symptom-free. Abdominal tumour unchanged in size and consistence. Vaginal examination revealed a small hard cervix, both lateral fornices were quite clear. It was difficult to be certain whether the tumour was the uterus or not. Operation was again urged, but refused as the patient felt perfectly well.

January 20th. Re-admitted with abdominal pain. Temperature 100°F. She had had bright bleeding for 2 days, with some dark altered blood to-day. Tumour as before, but now tender at the fundus. Cervix hard and not dilated.

January 28th. Temperature ranging from 99°F. to 101°F. Moderate abdominal pain, and some brownish, not offensive discharge *per vaginam*. Vaginally, a soft tender mass in the right fornix. White cells, 8,200 per c.mm.

February 18th. Very little change, but temperature swinging more widely lately. Red cells, 3,230,000. Haemoglobin, 60 (Sahli). White cells, 10,100. Complains now of much more severe pain, radiating to the rectum, with severe pain on defaecation. Vaginally, the mass is larger, extends into pouch of Douglas and fluctuates on pressure. Also palpable as a boggy swelling in the rectum. Cervix as before.

February 21st. Pain more severe. White cells, 19,500. A spinal anaesthetic was given to allow of adequate examination. A large soft mass in the posterior fornix rendered the cervix almost inaccessible. The mass was needled through the vagina, and only clear fluid (containing moderate numbers of pus cells on microscopy) was obtained. Drainage was therefore not attempted. Protruding from the os was what appeared to be a piece of umbilical cord, and offensive pus could be expressed by pressure on the fundus. The os was dilated to Hegar 15, and a rubber tube inserted for the injection of glycerin into the uterine cavity.

February 23rd. Temperature normal since dilatation, and severe pain relieved.

February 25th. Tube extruded.

February 28th. Vaginal swelling less marked and not tender. White cells, 10,700.

March 10th. Still nonfebrile. Had a sudden free discharge to-day with relief of pain.

March 23rd. Temperature raised every evening. Abdominal tumour unchanged, but the vaginal mass has almost disappeared. Weight, 68 pounds. Vaginal hysterotomy was performed under spinal anaesthetic, and the foetus removed piecemeal. All except some of the hand and foot bones and two ribs were accounted for, and some of these had been passed in the days preceding operation. Rubber tube left in cervix.

March 27th. Moderate haemorrhage round tube. Free pus discharge through tube. Red cells, 1,900,000. Haemoglobin, 40 (Sahli). Blood transfusion of 15 ounces.

Two days later the vaginal discharge became frankly faecal, and remained so for 5 weeks. The patient lost weight until she weighed only 56 pounds. Gradually the faecal fistula, which appears to be recto-uterine, closed, and the patient regained weight. By May 15th she was back to her normal weight, the abdominal tumour had completely disappeared, and the bowels were moving normally. She was discharged on June 4th, and at the date of writing weighs 73 pounds.

## Discussion

The ideal treatment for this patient, had immediate admission been possible, would probably have been Caesarean section. By the time treatment could be undertaken, however, the moment for this had passed. The diagnosis was presumably concealed ante-partum haemorrhage, but the prolonged retention of the foetus and the complete recovery in January made me somewhat uncertain of this diagnosis; rupture of the uterus and extra-uterine pregnancy having to be considered. Subsequent events, however, confirmed the original diagnosis. My inclination was to perform laparotomy in January, when all symptoms had disappeared, and to decide on the treatment according to the findings at operation. This the patient refused; moreover, the very bad effect which an unsuccessful operation has upon other patients, makes one very reluctant to press surgical treatment on native patients.

What precipitated the onset of the infection I am unable to say; but once it had occurred and a pelvic abscess had formed, Caesarean section was obviously out of the question. After waiting more than a reasonable time for the uterus to empty itself, the rather unorthodox procedure of vaginal hysterotomy appeared to be the only justifiable course. The operation was performed by the usual technique, the uterus being opened

longitudinally by an incision reaching well up into the body. The incision in the vaginal mucosa was closed without drainage and no trouble with parametritic infection was encountered in spite of the grossly infected nature of the uterine contents. Recovery undoubtedly dated from the operation, though convalescence was greatly prolonged by the development of the recto-uterine fistula, which I am inclined to attribute to the ulceration by a foetal bone rather than to the pressure of the drainage tube. Transfusion of blood was a life-saving measure on the first and probably also on the second occasion on which it was employed.

## Summary

A woman had a severe concealed ante-partum haemorrhage under conditions which made immediate treatment impossible. Labour failed to commence, and after a period of 4 weeks the patient was free of symptoms, but with the dead foetus still *in utero*. Repeated attempts at medical induction of labour were unsuccessful. Infection later supervened, but the foetus was still retained, until delivered by vaginal hysterotomy 22 weeks after the original haemorrhage. Convalescence was prolonged by the development of a recto-uterine fistula, but ended in complete recovery.

# An Unusual Tumour of the Vulva

BY

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MISS D. A., aged 29, consulted me in September, 1940, complaining of a "lump" in the vulvar region which she said had been present from birth. She had always had to wear a napkin "because of the lump." There was a tendency to incontinence but she always managed to get to the lavatory. I attended her mother when she was born on the 11th March, 1911, and the record in the Rotunda Hospital books reads: "Abnormality of vagina, rectum and bladder of congenital origin. Cloacal formation of rectum and bladder."

The child was re-admitted to the Rotunda Hospital, aged one year and 5 months, in September, 1912. The notes of the physical examination by Dr. Jellett were as follows: "There is a reddened cone-shaped tumour with rugae lying below the symphysis. There are two orifices at the summit of it and at the base behind two openings; one is behind the other and is in direct connexion with the intestine above. In the region of those behind there is a depression corresponding to the situation of the real anus. A pouch passes back to this from the abnormal anus. There are two urethral openings, one on each side of the mass, which latter is taken to be an inverted vagina with double uterus. The abdomen is full of faeces apparently at the sigmoid flexure which has become straightened out."

On the 27th September, 1912, in consultation with Mr. Heuston an incision was made backwards to the perineum from the abnormal anus to the site of the normal one. The sphincter was divided and the edges of the mucous membrane of the rectum were tied to the skin with interrupted catgut sutures. A large mass of faecal matter was removed with a blunt instrument, and finally an enema of olive oil was given. She was discharged apparently cured on 9th October, 1912.

Miss D. A. was a good-looking girl who seemed to be younger than her age. She said she had always been shy about this mass

FIG. 1

A and B = Crypts
C = Rectum

B.S.

FIG. 2

B.S.

and had never consulted a doctor, but now she wanted to get married and felt that the lump was a disability. Menstruation, heart, lungs, urine, were all normal. It was impossible to examine her without an anaesthetic. Under an anaesthetic a mass was apparent; it was an elastic yielding compressible swelling about the size of a Victoria plum; it was eroded and there were two crypts which did not admit a ureteral catheter. The mass was anterior to the anterior vaginal wall. The urethral orifice was to the left side of the mass. The vaginal orifice admitted a finger, but the rectal orifice was very distended and appeared to be inflamed. The perineum was absent and the vaginal and rectal orifices were separated only by a thin stratum.

Mr. Chance and Professor Jamieson kindly saw the case with me. The latter stated that the deformity did not follow any pattern of embryological error. He suggested that it might be a mammary tumour.

An intravenous pyelogram was done. The left kidney showed good function. The right kidney showed marked ptosis, irregularity of calyces. An X-ray of the pelvis did not show any bone change.

*Operation. 17th September,* 1940. I approached the operation with a certain amount of dread. Dangers to the bladder and the ureter seemed to be present. A circular incision was made around the protruding mass and a line of cleavage was found. A catheter was kept in the urethra and the bladder was found to be just above the mass. A thin cord was found running down the right side of the growth and was suspected of being the end of the right round ligament. The mass was of loose connective tissue and was excised. Some deep catgut sutures were inserted to close the cavity and the edges of the wound closed with continuous catgut sutures and a few of interrupted silkworm gut. A small drainage tube was inserted in the cavity.

*Pathological Report on the Excised Tissue by Dr. Bourke.*

To the naked eye the large mass is covered by squamous epithelium, but at two points, about the size of a sixpence and a shilling, the appearance is rugose and suggestive of the interior of the bowel. The smaller tumours are simple fibrous tissue covered by normal squamous epithelium. Microscopic sections of the smaller piece of tissue, said to be possibly the round ligament, show merely fibrous tissue and blood-vessels. The larger mass shows the rugose area to be typical bowel epithelium, with mucous glands and some inflammatory cells, below there are

muscle fibres arranged in bundles which suggest bowel wall. There are many thick-walled blood-vessels. Part of the tumour is covered by squamous epithelium. The condition is that of a congenital abnormality.

*Progress*: The patient's convalescence was almost without incident. The wound was somewhat slow in healing due to the development and supervention of a small septic spot which sloughed. The stitches were removed when the wound was healthy and the patient was discharged on 14th October, 1940, with instructions to return for re-examination in a month's time.

Examination almost a month later showed the vulva nearly normal. The vagina, however, was still very narrow, and dilatation was advised in the event of matrimony. The patient felt well, and expressed herself mightily relieved by the disappearance of the growth.

# A Case of Pseudo-ovarian Cyst

BY

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THE following case is considered worthy of report because of certain unusual features.

The patient was a Muslim female, aged 34 years, admitted to Queen Mary's Hospital on May 11th, 1940. The patient had had 7 children at term. The labours and puerperia of labour were normal. The youngest child was 8 years old.

On admission the patient complained of: A painless tumour arising from the pelvis in the midline, and which had been gradually getting larger for the past 2 years; an increasing painless menorrhagia of 1½ years' duration; and flatulent dyspepsia for 6 months.

Physical examination showed a fairly well-nourished middle-aged woman, slightly anaemic. Her mouth and throat were healthy, her circulatory and respiratory systems were normal; glands could not be felt and her blood-pressure was 120/75. Her urine was normal, and sterile on culture.

*Blood Count.*

Red blood corpuscles, 2,500,000; white blood corpuscles, 9,000; haemoglobin, 80 per cent; differential count polymorphs, 78 per cent; lymphocytes, 20 per cent; large mononuclears, 2 per cent.

*Abdominal Examination.*

*Inspection.* The abdomen was enlarged to the size of a full-time pregnancy, striae gravidarum were present, the swelling was greater anteriorly than in the flanks. There were not visible any enlarged veins, the skin was healthy, and the umbilicus was normal.

*Palpation.* A soft cystic tumour could be felt extending medially from the pelvis to 2 fingers' breadth below the ensiform cartilage and laterally partly into the flanks and iliac fossae.

The tumour was irregularly lobulated in outline, freely mobile from side to side in its upper part, but not movable from above downwards, a fluid thrill could be elicited. The measurements above the level of the umbilicus were greater than at its level, and the spino-umbilical measurements were equal.

*Percussion.* The note was dull over the tumour and resonant in the flanks.

*Vaginal Examination.*

A relaxed outlet with a certain amount of cystocele and rectocele. The urethra was normal. Bartholin's glands were not palpable. The vaginal vault was lower than normal.

The cervix was pointing forwards and the body of the uterus could be felt through the posterior fornix, slightly mobile. The tumour could be felt through the anterior and antero-lateral fornices and was fixed. The cervix was healthy.

*Provisional diagnosis.* Ovarian cyst.

On May 14th, 1940, the abdomen was opened by a median sub-umbilical incision. On passing a hand into the abdomen, the tumour was found adherent to the anterior abdominal wall below. The incision was extended to the upper limit of the tumour.

The adhesions were so dense as to necessitate removal, together with the tumour of a median strip of peritoneum, linea alba and recti muscles, from midway between umbilicus and pubes to the level of the pubes. The tumour could now be lifted out of the abdomen and the remaining attachments to the peritoneum in the region of the urachus were clamped and divided and the tumour, which did not possess a pedicle, was removed.

The uterus was normal in size, retroverted and mobile, and the Fallopian tubes and ovaries were healthy.

A ventral suspension was performed and the abdomen closed in layers in the usual manner.

The convalescence was without incident.

*Pathological report.* The tumour differs in no way from a pseudo-mucinous multilocular ovarian cyst.

*Microscopic report.* Cysto-adenoma.

The interesting feature in this case was the presence of a tumour with all the characteristics of a pseudo-mucinous cysto-adenoma of the ovary, and yet both ovaries were intact and healthy. The only attachments of the tumour were to the

anterior abdominal wall. It becomes difficult to explain the existence of an ovarian tumour attached to the peritoneum in the vicinity of the urachus. Four possibilities suggest themselves to me:

(1) That the tumour originated on the surface of one of the ovaries, became adherent to the anterior abdominal wall, and later lost its connexion with the ovary. Against this suggestion is the fact that at no time were there any symptoms of pain or internal haemorrhage which one would expect, had there been a breaking off of the tumour from the ovary; nor, apart from adhesions to the anterior abdominal wall in the midline, were there any signs of intra-abdominal peritoneal adhesions, as one would anticipate, had there, at some previous time, been intra-abdominal haemorrhage.

(2) The second possibility is of the detachment of ovarian anlage during the embryonic period; so that a portion of ovarian tissue developed in an ectopic site in the neighbourhood of the urachus.

(3) That the tumour developed from a metaplasia of peritoneal cells in the region of the urachus and took on characters of ovarian tissue.

(4) That the tumour developed from the urachus. Against this possibility is the fact that the urachus could be distinguished in the strip of peritoneum which was removed with the tumour.

So far as the literature is concerned I have no knowledge of any such tumour being previously reported, and the opinion of other gynaecologists would be interesting as to the possible origin of this tumour, which, for want of a better name, I have reported as pseudo-ovarian tumour.

# A Case of Vesico-vaginal Fistula of Four Months' Duration treated by In-dwelling Catheter

BY

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THE successful treatment by non-operative measures of a vesico-vaginal fistula about $4\frac{1}{2}$ months after its occurrence seems to me to be worthy of record.

F. J., aged 35 years, was admitted under my care on 22nd February, 1939, complaining of incontinence of urine. She had noted her symptoms shortly after an abdominal operation in November, 1938. I was able to obtain access to the operation notes; a subtotal hysterectomy and right salpingo-oophorectomy had been performed on 3rd November, 1938, by a competent gynaecologist. The uterus had been irregularly enlarged by fibroids, one large fibroid on the anterior wall of the uterus extending outwards between the layers of the right broad ligament. Convalescence had been uninterrupted except for a temperature of 100.2° F. and 100° F. on the first and second nights after the operation.

On examination of the patient, there was marked excoriation and numerous ulcers and small abscesses around the vulval area and on the upper part of both thighs; the vagina was reddened and in the anterior fornix to the right of the middle line and just in front of the cervix there was a fistulous opening about $\frac{1}{4}$ to $\frac{1}{2}$ an inch in diameter. There was entropion of the edge of the fistula and no apparent redness or pallor around the edge. Indigo-carmine was injected and urine was seen passing from the bladder into the vagina.

As a preliminary to operation the patient was given frequent baths, and calamine lotion and boracic powder were applied over the excoriated area. The patient was also given a urinary antiseptic. The condition of the vulva improved slowly, and the lotion was replaced by an ointment, but 3 weeks later, as the vulval condition did not yet permit of operative interference, I

decided to hasten matters by inserting an in-dwelling catheter through the urethra and established continuous suction drainage of the bladder. The catheter was inserted on 11th March, 1939, that is 128 days after the hysterectomy, when presumably the bladder had been damaged. The catheter was kept patent. On 24th March I examined the patient again and to my surprise found the fistulous opening in the vagina closed. I made a cystoscopic examination and saw a small puckered area in the wall of the bladder but a fistula was not seen. Methylene blue was then injected into the bladder but none passed through into the vagina.

The patient was seen again one year later in February, 1940. Urinary symptoms were absent. A cystoscopic examination was again made. There was a small puckered area on the base of the bladder; a fistula was not seen. The ureteric catheter passed easily into the right ureter.

## Commentary

Vesico-vaginal fistula is in this country a comparatively rare condition nowadays. In the older textbooks of gynaecology the treatment of this condition occupies many pages and all these writers stress the wisdom of waiting to ensure that nature has had time to effect a spontaneous cure before operative treatment is undertaken. Many cases are described in which the fistulous opening has been large enough to admit two fingers and yet spontaneous cure has resulted. The time of election for operation in post-partum cases is given as 6 to 8 weeks after delivery, since by this time the edges of the wound are vascular and firm while later cicatrization and fibrosis around the fistula add to the difficulties of the operation. The time of election for post-operative cases would for similar reasons be the same as that for post-partum cases. It is reasonable also to suppose that by 6 to 8 weeks the mucous membranes of the vagina and bladder will have united and that, therefore, spontaneous cure is unlikely to occur, but union of the edges may occur apparently much later or the treatment adopted in this case could not have been successful.

I am indebted to Dr. Allen Daley, Chief Medical Officer, London County Council, for permission to record this case.

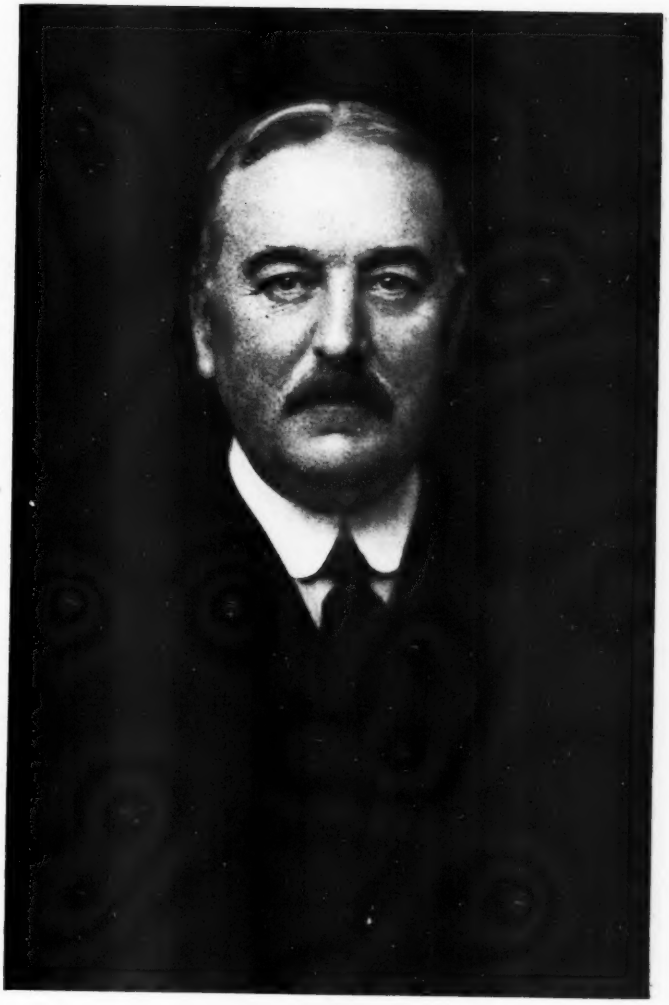
# Obituary

## Herbert Ritchie Spencer

On August 28th, Dr. Herbert Spencer passed peacefully away, in his 82nd year, at his home in Bickenhall Mansions, surrounded by his beloved collection of books, lacquer and other art treasures, which he had resolutely refused to desert however ruthless the Nazi blitz on London. Mercifully it had left his last few weeks in comparative peace. He had outlived most of his intimate friends, others were debarred from visiting him, but he was tenderly cared for by his faithful and devoted valet and his wife. His mortal remains were cremated at Golder's Green, the ashes being scattered on the adjacent Garden of Memory.

Born at Atherstone, Warwickshire, he was the second son, of a family of seven, of Henry and Harriette Spencer. His father, a building contractor, was associated with Thomas Brassey in the construction of the early English railways. This may explain his grandmother's friendship with the great Victorian philosopher (after whom Dr. Spencer was named), who had been a young engineer on the London-Birmingham line. At Atherstone Grammar School he received a sound classical grounding from which he derived much benefit and pleasure all his life, both as a service of apt quotation and from translating, into English verse, many of the poems of his favourite Latin authors.

Here he also imbibed the rudiments of French and German, which, later on, together with Italian, he studied, in order to enjoy their literature, both medical and general. He was even able to address Congresses abroad and make good and amusing after-dinner speeches in fluent French or German. Early in his medical course he acquired shorthand, and ever afterwards made great use of it. It facilitated the recording of his case notes, both hospital and private; these were remarkable for their completeness and accuracy, and, moreover, were made even more lucid by drawings, sometimes in colour. He much preferred to place on record "full and careful observations from which deductions could be drawn or on which working theories could be based, than to write text-books" possibly "of ephemeral value."



HERBERT R. SPENCER

In 1879 he entered University College, London, qualifying M.R.C.S. and L.S.A. in 1883. He graduated M.B., B.S. (Lond.), with honours, in 1884, and took the M.D. in 1886. In 1899 he was elected F.R.C.P. He was Obstetric Assistant, House Surgeon and House Physician to the hospital in 1883-6, and broadened his outlook on life by voyaging, as medical companion to Earl Bantry, to New Zealand, Australia and India, and in travelling in Germany and Switzerland with the Earl of Dalhousie.

In 1887 he was elected to the staff as Assistant Obstetric Physician, under John Williams, "my teacher, master, colleague and friend for forty years." The next 38 years of his life were devoted to the practice and teaching of his specialty at his beloved hospital. The title of Professor of Obstetric Medicine was given him in 1893. His retirement from the staff in 1925 was greatly regretted by his colleagues and students: it elicited a glowing appreciation in the College Magazine.

He was an excellent lecturer and teacher, lucid and easy to follow, and sound; all his classes were crowded. He took a great interest in his clinical clerks and residents.

As an operator he was methodical and careful; he made no bid for brilliancy. The outstanding success of his operations depended largely on his accurate diagnosis, his strict use of antiseptic and aseptic precautions and the elaborate care with which patients were prepared for operation. In matters of technique he strenuously urged the advisability of total hysterectomy for fibroids, to exclude the risk of cancer in a cervical stump, the use of silver wire in closing fistulae and the avoidance of catgut, for fear of tetanus.

His genius for clinical observation was early manifest. In 1886, he reported in the *Lancet*, a case of cerebellar tumour in which, as well as ocular nystagmus, he had observed continuous rhythmic movements of the pharynx and larynx. He used the title "Pharyngeal and Laryngeal Nystagmus." He was pleased when French authors, in 1937, referred to the "Syndrome de Spencer."

In 1889 he initiated a long series of communications (there are 43 in the general index) to the Obstetrical Society of London with a short paper on "The diagnosis of Placenta Praevia by palpation of the abdomen;" this excited much interest and discussion. In 1891 appeared "Visceral Haemorrhages in Stillborn Children," a classical work, fully tabulated and richly illustrated, based on 130 autopsies: he was personally respons-

ible for the examinations, the microscopic sections and the drawings. In 1892 he wrote, in the *Lancet*, on "Intravenous injection of normal saline for grave haemorrhages of midwifery." He claimed to have had, in 1888, the first successful case. For the purpose he suggested and had prepared sterilized sealed glass tubes of weighed sodium chloride. In 1893 he read a paper to the Medical Society of London, on "A first series of fifty ovariotomies;" in this he stoutly maintained "A plea for the performance of ovariotomy by Obstetric Physicians." There was only one death in the series, the lowest rate then published. For this, he characteristically gave the credit to "my predecessor (John Williams) whose methods I have followed." In 1933, at the Royal Society of Medicine, he analysed the case records of his whole series of 658 ovariotomies. In 1934, before the History of Medicine section, he read "The History of Ovariotomy;" an amplification of the address he had given in 1909, before the American Gynecological Society.

In 1925, he published a small book on "Caesarean Section;" a full account of his own technique and his usual tabulated analysis of his cases—128 with 4 deaths—is preceded by a concise historical study. His well-known views on "Total Abdominal Hysterectomy for myoma of the uterus, with special reference to cancer of the cervix after subtotal operation," were fully expounded in the *British Medical Journal*, in June 1932.

But it is from his public lectures and orations and presidential addresses that we can learn most of the man and his achievements. These have been published in book form and are of permanent value. They are now given in chronological order, with occasional characteristic quotations.

1894. An introductory address to the students of the Faculty of Medicine of University College. This is a surprisingly matured discourse with much sound advice. Already he is stressing the value of accurate note-taking: it "is as necessary for advance in medicine as accurate observation, of which it is indeed a repetition in permanent form." He claimed for medicine "a fascination which no other profession possesses:" "observation," he said, "is of little value unless it is recorded; nor of value then unless the record can be found," and "drawings afford one of the best means of ensuring accuracy." (His own hospital and private notes are perfect examples of these requirements.) Finally he tells students that "by lectures you may become learned, but not honest, sympathetic, and kind—qualities essential to success," and "it will be your own fault if you

are not among the most respected members of the community in which you live," for "according to the way in which you perform your duties will you gain or lose respect."

1920. The Lettsomian Lecture, before the Medical Society of London (of which in 1923 he became President), on "Tumours complicating Pregnancy, Labour and the Puerperium." In this he analysed 55 cases, with one death. (An appendix was published in the *British Medical Journal*, in 1925, recording 8 additional cases, also with one death.) All his cases of uterine fibroids, ovarian tumours, and cancer of the uterus complicating pregnancy are fully described and carefully tabulated.

1921. The Harveian Oration, before the Royal College of Physicians, on "William Harvey, Obstetric Physician and Gynaecologist:" a scholarly piece of work which established the fact that Harvey had also been the first writer on obstetrics and gynaecology in this country.

1924. The Lloyd Roberts Lecture, at the London Medical Society's rooms, on "The Renaissance of Midwifery." To develop his theme he gave particulars of the first books on Midwifery in Germany, France, Italy and England. The lecture was published with reproductions of many of the title-pages and illustrations of these books.

1927. The Fitzpatrick Lectures, before the Royal College of Physicians, London, on "The History of British Midwifery from 1650 to 1800." This was the first detailed account of the work of early British obstetricians. It involved extensive reading, not only of their printed works but of many manuscript lectures hunted down in various libraries. The importance of the bound volume with its nine portraits and many valuable footnotes and two appendices cannot be overestimated.

1929. A lecture on "Medicine in the days of Shakespeare," delivered at University College, London, fills one with amazement at the erudition it discloses.

In 1931 he gave the Inaugural address to the Midland Medical Society, at Birmingham. In this review of "Obstetrics and Gynaecology in the last fifty years," he briefly described the advances in practice that had been made: "unsurpassed," he claimed, "by those of any other branch of Medicine." His own share was a considerable one. To take one instance: he was a pioneer in routine antenatal care; "from the year 1887," he said, "I never attended a private lying-in patient without making an abdominal and vaginal examination, usually about the thirty-fourth week, to determine the size and shape of the

pelvis and the position of the child; and for more than thirty years I conducted a class every week in which students were instructed in these examinations" (a succession of U.C.H. students greatly valued these classes, which were skilfully illustrated by drawings in blue pencil on the large window panes.) His method was "based on the great work of Pinard, le palper abdominal." This was fully described by Spencer, with beautiful illustrations, in *The Illustrated Medical News* of 1890. He believed that the cost of his illustrations ruined the journal. It would be well if the article could be reproduced.

He was the last President of the Obstetrical Society of London, from March 6th to its last meeting on July 3rd, 1907, when it became merged with other societies in the Royal Society of Medicine. His inaugural address (on March 6th) is, as are the majority of his addresses, still well worthy of careful study. He applied most characteristically Francis Bacon's diatribe in "The Advancement of Learning" against "vain words," "vain matter," and "deceit or untruth" to some of the medical publications of the day. He then pleaded for the "careful patient collection of facts and judicious comment upon them." Finally, after referring to the impending formation of the Royal Society of Medicine he mentioned his own hope that all the Medical Societies and the two Royal Colleges would, someday, unite to form a Royal Academy of Medicine, to be housed in a building worthy of the English medical profession.

He then became the first President of the Obstetrical and Gynaecological section of the new society, occupying the chair from the first meeting in October 1907 until July 1909. In his valedictory address he regretted that it had been decided, on account of space, to omit obituary notices from the Proceedings, for, he said, "some of the most valuable contributions to the history and biography of medicine have been originally made to the transactions of learned societies." He then anticipated the formation of a section of the History of Medicine. Over this he presided in 1928.

He was one of the most regular attendants at the meetings of these two sections, to which he made many valuable contributions both in original papers and discussions.

His reverence for the memory of his dead heroes was very real. He was an active member of the William Harvey Memorial Committee which restored the tower of Hempstead Church, Essex, where Harvey's remains were deposited. In the summer of 1933, he addressed, at Holme Hall, Bakewell, Derbyshire,

a large gathering met to commemorate the bicentenary of the birth, at Bakewell, of Thomas Denman, who, Dr. Spencer stated, "at the age of 50 years was the most distinguished and esteemed of British Obstetricians." He then exhibited an inscribed stone tablet, "the gift of British Obstetricians," which was subsequently placed in the chancel of the parish church.

In July 1939, the writer had the great pleasure of accompanying Dr. Spencer to Holland on a pilgrimage to the tomb of Jason à Pratis (or Pratensis), whose "De Pariente et Partu" Spencer had translated and presented to the library of the Royal College of Physicians. He had been buried in the Cathedral of Saint Lievens at Zierikzee. But a great fire in 1828 had gutted the building and neither tomb nor bust could be found. However, the written record of his death, on May 24th, 1558, was discovered in the Bureau of Archives at Middelburg.

Out of respect for this form of hero-worship of Spencer's, pains have been taken to ensure the accuracy of the details of his life and opinions, which may be valued by students of British midwifery in distant years to come.

They should also know that he was a man of large physique, with a commanding eye and resonant voice, his forthright speech proclaiming the firmness of his opinions. He liked company and was a familiar figure at medical gatherings in London and at Congresses in the provinces and on the Continent.

For recreation he enjoyed shooting and fishing and the study of bird-life in Regent's Park or in the country. He read much and collected a notable library, especially rich in old works on midwifery; he was particularly proud of his seventeen editions of Scipio Mercurio's "La Commare." It also contained folios of the classics and many famous works on Natural History. In his search for knowledge on the matter he had in hand, he explored the shelves of the British Museum and of the various medical libraries, to which, indeed, he was one of the most frequent visitors. He thus acquired a most profound acquaintance with the literature of his subject, and nothing less satisfied him. He had presented many valuable volumes to these libraries, and now he has bequeathed "all my old medical books and such other as they desire to the Royal College of Physicians," and any other medical books to University College Hospital. He was very generous towards causes which appealed to him and did much quietly for cases of real need. He was a member of the Committee of the British Medical Benevolent Association to

which he has bequeathed the residue of his estate, after making large bequests to the Royal College of Physicians, University College Hospital and the Medical Society of London.

A judge of wine and food and a good cigar, he was a thoughtful and genial host at his club or his bachelor quarters. He was not easily approachable, but he made staunch friendships, which he often delighted to cement by letters in rhymed verse and decorated with dainty drawings.

His aloofness from the new British College of Obstetrics and Gynaecology must be referred to. He refused not only to become an original Fellow, but even, in private conversation with a friend, to consider the acceptance of a proposed Honorary Fellowship. This was partly due to an innate love of opposition—to accentuate his invariable determination to prove the worth of an innovation before he accepted it—and partly to his zealous devotion to the Royal College of Physicians and his strong desire for a British Academy of Medicine. He would not see that the formation of a College to promote the study and advancement of "the third great division of medical practice" (his own designation, in 1893) might well be a stepping stone to the birth of such an academy. Latterly he was frankly surprised at the success of the new Royal College and he became more and more impressed by the public value of its achievements.

Academic distinctions of which he was justly proud were Honorary Fellowship of the American Gynecological Society, of the Obstetrical Society of Edinburgh and of the Société d'Obstétrique et de Gynécologie de Paris and of the Société Belge de Gynécologie et d'Obstétrique. Perhaps the one he chiefly valued was the Honorary LL.D. of the University of Aberdeen, and particularly the recognition by the public orator of the fact that "for over forty years he had been an inspiring and dominating force in Obstetrical Science in this country."

MILES H. PHILLIPS

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## An Appreciation

WITH Herbert Spencer an important figure in British gynaecology has passed away and a man whom everyone respected for his outstanding honesty—even a man who did not agree with him never suggested that Spencer ever did anything mean or by

subterfuge. His arrival at a meeting of the Royal Society of Medicine often meant that some entertainment was in store, for he loved a fight and had no hesitation in going into the fray with a gusto which caused a certain amount of amusement. He was a formidable opponent since he had an unrivalled knowledge of the literature which he could quote at length from memory as well as an especially large clinical experience, as he was in the unusual position of having been elected to the staff of University College Hospital at the age of only 27.

His pet subjects to speak on were that subtotal hysterectomy ought to be given up ("I have not performed such an operation for 30 years"), that nearly all cases of extra-uterine gestation could be treated without operation, that silver wire should be used in the repair of fistulae and that catgut should not be used for any purpose in surgery. He was so sure that his opinions were correct that he rarely changed them, and the advent of boilable tubes of catgut did not shake his view that their use would result in tetanus.

The only occasion which I can remember when he did give up one of his opinions was when he abandoned the treatment of carcinoma of the cervix by high amputation with the cautery in favour of the Wertheim hysterectomy, and was the second man in Britain to perform one. He was an outstanding authority on gynaecological histology and in his beautifully direct fashion would give a definite opinion on a difficult slide when others were discreetly avoiding giving any opinion at all. He offered his resignation as a member of the Pathology Committee of Obstetrical Section in 1937, on the grounds that he was no longer up-to-date, but the resignation was unanimously refused by the Council. His pleasure at this compliment was obvious.

He was President of the Old Students' Association and always had a crowd round him at Old Students' meetings, and it was almost a routine for him to be called on to make an extra speech at the annual hospital dinners. His French and German were fluent and it was a pleasure to hear him address a visiting Society of French gynaecologists in their own language without hesitation and with a perfect accent.

From a student's point of view, his skill as an artist was rather a drawback because it amused him to draw finished pictures of tumours or of the attitude of the foetus *in utero* when a quick rough diagram would have sufficed for teaching purposes. However, his drawings were extraordinarily life-like and at examinations his blotting paper was regularly removed by the

porters who wished to keep it because of the caricatures of the candidates which he had amused himself drawing during the viva voces.

He was keen on fishing and shooting and for some years had a shoot in Norfolk. He used to say that as a very small boy he took his first shot at a chicken in his father's garden. Although he liked fishing and shooting, he did not play games, nor did riding or such things as swimming appeal to him. Many were surprised that he did not move to the country when he retired from practice, after 40 years in Gower Street, Mansfield Street and Harley Street, but he preferred to go only as far as Baker Street, where he lived for the last 15 years of his life. He was a good judge of wine, collected Japanese and Korean antiques and was an authority on old books, especially old medical books.

A big man both physically and in spirit, we shall look in vain for another quite like him.

C.W.

# ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The Quarterly Meeting of the Council was held in the College House on Saturday, July 26th, 1941, with the President, Professor W. Fletcher Shaw, in the Chair.

Professor W. Fletcher Shaw, M.D., Ch.B., F.R.C.P., F.A.C.S. (Hon.), was re-elected President to take office in October next.

The following officers were also elected:—

*Vice-Presidents*:
Eardley Holland, M.D., B.S., F.R.C.P., F.R.C.S.
Charles Gibson Lowry, M.D., F.R.C.S.I.

*Honorary Treasurer*:
John Prescott Hedley, M.A., M.B., M.C., F.R.C.P., F.R.C.S.

*Honorary Secretary*:
George Frederick Gibberd, M.B., M.S., F.R.C.S.

*Honorary Librarian*:
Wing Commander Frederick Roques, M.A., M.D., M.Ch., F.R.C.S. (R.A.F.V.R.)

*Honorary Curator of Museum*:
Aleck William Bourne, M.A., M.B., Ch.B., F.R.C.S.

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The following candidates were elected to the Membership:

Gavin Boyd, Glasgow.
David Spencer Foster, Sheffield.
Edward Gledhill, Batley.
Constance Eileen Peaker, Leeds.
Kathleen Marian Robinson, London.
Katharine Churchill Rogers, London.
Richard Xerxes Sands, London.
Violet Evelyn Augusta Sykes, London.
George Wynn-Williams, London.

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The following were admitted to the Fellowship of the College:

Norman Llewellyn Edwards, Derby.
Wentworth Alexander Taylor, Birmingham.
Robert Watson, Northampton;

and to the Membership:

Jack Joseph, London.

# BOOK REVIEWS

"The Periodicity and Cause of Cancer, Leukaemia, and Allied Tumours: with Chapters on their Treatment." By J. H. DOUGLAS WEBSTER, M.D., F.R.C.P.E., F.F.R., Honorary Director, Meyerstein Institute of Middlesex Hospital. London: 1940. Baillière, Tindall and Cox. Price 12*s*. 6*d*.

COMING from the pen of a well-known authority on radio-therapy, this volume deserves the serious consideration of those who are engaged on researches into the causes and treatment of neoplastic diseases. Although Dr. Webster gives due reference to the work of previous observers, his study of his cases shows deductions evolved from his own scientific attitude of mind, and he gives a free criticism of all the statements which he puts forward. Valuable case records and statistics are given to support the results of an investigation of a subject which always demands criticism upon the publication of new ideas. Rhythm, he says, is characteristic of all motion or action that is not in stable equilibrium, and many diseases show a rhythmic or periodic type of recurrence. An example of this is influenza, reference to which has been made by the author in a previous publication.

He is of the opinion that neoplastic diseases belong to the virus type, as cancerous growths show inclusion and elementary bodies. In a previous communication he also discusses the influence of sun-spot cycles upon the periodicity of disease as well as upon biological cycles, such as oestrus.

The present research is the result of a prolonged study of over 800 cases of neoplastic conditions in which the periodicity of recurrences has been manifest. Dr. Webster states that tumour growth is not in the nature of a progression, but that it is characterized by phases of activity, followed by (usually longer) phases of quiescence as seen in untreated cases, and in patients who have not had any subsequent treatment owing to apparent cure. His results lead to a definite theory as to the possibility of defining the almost exact date of recurrence, and the possibility of appropriate preventive treatment, provided the patient is kept under observation at regulated intervals. His patients showed a great diversity in their clinical and periodicity histories, no two patients had exactly similar sequences. Three main groups however can be classified.

*Phase* 1. A standard or full period of approximately 33 weeks, with a plus or minus margin of 3 weeks' duration. Cancer is mainly included in this monophasal type. *Phase* 2. A half-period of 16½ weeks. Sarcoma is an example of this diphasal type, also leukaemia, and Hodgkin's disease. *Phase* 3 is the multiple of 1 and 2. In most cases the recogni-

tion of the periods is easy when the history is fully investigated, but the possibilities of variation are immense. The prognosis is worse in the diphasal type. Recurrences are due to more active infection or to lessened resistance, and the longer the periods of intermission the better the prognosis. Accuracy as to the probable date of recurrence can be made to within a month. The dates of recurrence can be foretold more easily in cases of oral or skin growths than in those of the breast, skin or cervix. The various methods of treatment, whether surgery, radium or X-ray therapy, do not affect the periodicity. The recurrence is in the cancer cell itself. "Periodicity is a characteristic which is independent of changes in the site of environment." If patients with long periods of periodicity manifest half-periods or multiples, it means that the condition has become more serious, and even fatal in its termination. Weekly observations upon patients, if possible, should be made before or during the active peaks of the periods. If a record is kept of the date of recurrence, a forecast can be made of the next probable period based on a table of dates of periods or half-periods as demonstrated by the tables and charts in the appendix.

The various factors which may affect periodicity are discussed and figures are appended to show that there is a seasonal periodicity with a maximum in the months of January to March. Trauma may affect some cases, and influenza seems to have an influence upon recurrences.

The influence of carcinogenic agents is mentioned, including also that of benign tumours, with regard to the question of subsequent immunity to malignant growths. Internal factors require much further research as the author points out. Ovarian hormones are related, especially in cases of breast cancer, and research is required into the influence of ovarian hormone injections as a "preparer" of cancer.

The author suggests that the influence is not an ovarian one alone but is pluriglandular. Several of the patients showed an interaction of menstruation with the neoplastic rhythms, but this and other ideas require much further study. Age does not seem to affect the periodicity of recurrences, and this statement is of interest as the experience of most surgeons and radiologists is that cancer in older women is of slower growth than in some cases of young women. Examples of this are found in breast cancer, and also in uterine growths in which response to treatment may be disappointing. Hormone activity therefore may be considered as a factor from a clinical point of view.

In treatment the factor of periodicity is of importance. Surgery is more likely to cause local or distant metastases if applied in the active phase, and better results are obtained if operative measures are carried out in the quiescent interphase. Even biopsies, as pointed out by Dr. Webster, have their element of risk in the active phase, as there is the danger of cellular and virus dissemination.

In treated cases we find it sometimes difficult to decide between a metastatic recurrence and fibrotic changes due to previous irradiation, or to inflammatory induration. The study of periodicity would therefore help

in the diagnosis of recurrence due to neoplastic activity if it occurred at the time of a forecasted maximum or peak. The untreated cases showed the same type of periodicity as the treated. Death is most likely to occur at the time of the theoretical maximal peak or close to it.

The outstanding feature of this research is the study of the predictable periodicity of recurrences of cancerous growths, and it means that once a patient has come under treatment a careful follow-up is necessary for many years; the date of the possible recurrences should be recorded and forestalled by prompt and adequate treatment. The best results are obtained by X-ray therapy when applied to likely areas of recurrence in the weeks before there is any clinical evidence of the disease. Not more than 10 per cent of cases of cancer survive for more than 10 years. Radio-therapy in combination with surgery or radium has greatly added to the possibility of lowering this death-rate if applied early.

Dr. Webster's work, by a study of the periodicity or recurrences, brings a refreshing and more hopeful outlook to the problem of the treatment of neoplastic growths. His work is of interest also to biologists and epidemiologists. The volume contains numerous photo-micrographs, charts, and a useful bibliography.

A. Louise McIlroy.

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"The Nursing Couple." By Merrell P. Middlemore, M.D. London: Hamish Hamilton Ltd. Price 7*s*. 6*d*.

This is an interesting and unusual study of the psychology of the mother and child during lactation, with an introduction by Dr. Edward Glover, the well-known Director of Research in the Institute of Psycho-Analysis. In his introduction Dr. Glover describes the book as the "first serious attempt made by a qualified Psycho-Analyst to study systematically, and at first hand, the psychic suckling situation between mother and child." He considers that Dr. Middlemore's results deserve the serious consideration of all who are interested in child welfare including doctors, midwives, and children's nurses; and also that the mother herself will be immensely helped and encouraged by Dr. Middlemore's book. From personal experience I can endorse this view, having lent the book to two highly intelligent women, neither of whom wished to suckle her child, and asked them to read it, and give me their opinion. I observed a change in their attitude to their infants, both having read the book with the greatest interest, and in each case lactation was successfully established, and the mothers were, at the end of two months, managing their babies well, and enjoying the process of suckling.

Dr. Middlemore is a stern critic of those in attendance upon the "nursing couple," particularly of the midwife and maternity nurse. She observes that "Suckling is further complicated in the human species by an influence that does not obtain among other mammals; the ministrations of doctor and nurse, or whoever helps the mother through the

days following childbirth." As a result of these influences external to the " nursing couple " she considers that their mutual adaptation is necessarily modified, whether it be advanced by sympathetic nursing or delayed by misguided interference.

The various difficulties arising in connexion with breast feeding are fully described while the chapters dealing with unsatisfied suckling merit close study.

The role of the midwife or nurse and their emotional attitude to the " nursing couple " and their behaviour are explained and criticized. Dr. Middlemore considers that in many cases the treatment of nursing mothers by doctors and nurses often lacks common sense, and intuition, but that when attendants show obtuseness it arises as often from emotional difficulty as from lack of skill; less rigidity of technique is advocated as no " nursing couple " are alike. Dr. Middlemore suggests that " A general technique of nursing which is fixed and unadaptable works out badly, and indicates that the nurse has not benefited by her clinical experience of different kinds of ' nursing couples.' " She considers it permissible when starting lactation to direct suckling by means of a standard technique but that the wise nurse will adapt this later as need arises. Undue strictness and too vigorous handling indicate nervousness, and over anxiety on the part of the attendant to make the child feed satisfactorily. I would add to Dr. Glover's suggestion " that every mother who can afford it should buy three copies, one for herself, one for the doctor, and one for the midwife," that this book would form a most valuable addition to the library of every midwifery school.

M. W. S.

# Review of Current Literature

*Director*: FREDERICK ROQUES, M.A., M.D., M.Chir. (Cantab.), F.R.C.S., F.R.C.O.G.

THIS Review contains the lists of contents and abstracts of the more important articles from the journals with which the "Journal of Obstetrics and Gynaecology of the British Empire" exchanges.

The Review of Current Literature has kept the readers of the Journal in touch with current literature throughout the world; owing to the war many journals with which the *Journal of Obstetrics and Gynaecology* previously exchanged are no longer received. At the end of the year an Index of all the subjects contained in the articles of the journals reviewed is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology, and Biochemistry.

LIST OF ABSTRACTORS

J. LYLE CAMERON, F.R.C.S.; W. E. CROWTHER, M.B.; R. H. B. ADAMSON, M.D.; B. JEAFFRESON, F.R.C.S.; P. MALPAS, F.R.C.S.; T. N. A. JEFFCOATE, F.R.C.S.; MEAVE KENNY, F.R.C.S.; JANE H. FILSHILL.

## The Lancet

March 1st, 1941.

*A hundred cases of breech presentation. Allen Gardner, Margaret Jackson and L. N. Jackson.

March 15th, 1941.

*Bacillus lactis aerogenes infection in the newborn. Jean M. Cass.

March 22nd, 1941.

*Prolactin as a specific lactogenic hormone. S. J. Folley and F. G. Young.

May 3rd, 1941.

*Prevention of experimental fibroids by a cortical hormone. A. Lipschutz and L. Vargas, Junior.

June 21st, 1941.

The nature of disease in infancy. J. C. Spence.

*A pelvic hydatid cyst. E. L. Nicholson.

### A Hundred Cases of Breech Presentation.

The authors report a series of a hundred breech deliveries from hospital and private practice. There was no maternal mortality, but the infant mortality, when delivered through the natural passages, was 8 out of 27 hospital cases (30 per cent), and 9 out of 36 private cases (25 per cent). Of these 17 still-births, 4 were the children of multiparae. On the strength of this experience, the authors state that a breech delivery is a hazardous procedure, and that it should be less common than it is. Although they agree that version should be performed when a breech presentation is diagnosed during the antenatal period, they then state that Caesarean section at term is the method of choice when version has not been carried out. They believe that a mother, when delivered by section, is not put off subsequent pregnancies: whereas a long trying labour, especially when a living child has been obtained, acts as a deterrent.

One can hardly believe that these views will have universal acceptance.

### Bacillus Lactis Aerogenes Infection in the Newborn.

This report describes how 5 infants, between the third and ninth days of life, developed acute infection by the bacillus lactis aerogenes. These 5 infants belonged to a group of 22 whose mothers had been segregated for puerperal infection. The initial stage of the disease was insidious, and was characterized by the passage of relaxed yellow stools which were not unduly frequent. There was a reluctance to take feeds, an occasional small vomit and stationary weight. The colour was poor, and the extremities felt cold. This initial stage varied in duration from 12 hours to 4 days, and the fifth child to be affected recovered spontaneously at this stage. The toxic stage followed suddenly. The colour was greyish-blue, and the extremities were very cold. There was a slight rise in temperature but the child did not look sunken-eyed as in gastro-enteritis. The motions were frequent, green and watery; they contained no blood or mucus. One child died at this stage of acute respiratory embarrassment, and at autopsy a pure culture of the organism was obtained from the cut surface of the lung. Another child recovered quickly from the second stage, but later developed mild staphylococcal and dysenteric infections, but this did not affect its general condition. Two other infants made dramatic recoveries, after being extremely ill for several days. In both cases vomiting ceased after this improvement and the children took their feeds better, but the stools did not return to normal for about another week. About 36 hours after this improvement had set in, both children became pyrexial from staphylococcal infections of the subcutaneous tissue. Both progressed satisfactorily but one died suddenly after a convulsion at the age of 25 days. At autopsy a pure growth of bacillus lactis aerogenes was obtained from a soft thrombus of the umbilical vein.

### Prolactin as a Specific Lactogenic Hormone.

Folley and Young review recent research on the lactogenic hormones of the pituitary, and they come to the conclusion that the assumption formerly

made, that the anterior pituitary lobe secretes a single lactogenic hormone, is not correct. Purified preparations of prolactin are incapable either of initiating milk secretion in the hypophysectomized guinea-pig with suitably prepared mammary glands, or of stimulating milk production in the cow in declining lactation under conditions in which crude pituitary extracts are effective. The effectiveness of prolactin has been largely based on the hypertrophic response of the crop gland of the pigeon.

Clinical reports on the use of prolactin preparations for the purpose of stimulating lactation in women are conflicting; some successful results have been reported by some observers. The authors point out that a lactating woman, whose milk yield it is desirable to increase, is much more like a cow in declining lactation than a pigeon. Therefore, they are of opinion that it is important to measure on mammals the true galactopoietic activities of extracts destined for clinical use.

### Prevention of Experimental Fibroids by a Cortical Hormone.

In previous papers the authors have reported successes in preventing the growth of uterine fibroids produced by a prolonged administration of oestrogens. These were completely prevented by the simultaneous administration of quantities of testosterone propionate 50 times greater than those of the esterified oestradiol, or by quantities of progesterone 150 times greater than those of the oestrogen. They found that the technique of implanting tablets of progesterone under the skin was the most economical way of preventing the experimental production of fibroids by oestrogens.

Cortical hormones were suggested to the authors because of the chemical similarity of desoxycorticosterone to progesterone, and with the hope that it would be less harmful to the human body than either testosterone or progesterone. From their experiments they found that uterine fibroids were completely prevented and that this was achieved with a quantity of desoxycorticosterone of only 3 times the amount of oestrogen.

### A Pelvic Hydatid Cyst.

Nicholson describes a case in which a cystic swelling in the lower abdomen was found, at operation, to be a hydatid cyst. It was diagnosed as a common ovarian cyst, but an unusual thrill was noted on bimanual examination. At the operation the cyst was found to be covered by adherent omentum, and on separation of this the uterus, ovaries, Fallopian tubes, and broad ligaments were seen to be quite normal. The mass was difficult to remove and, during the separation of its wall from surrounding structures, an opening was made in its capsule and a soft mass, like a jelly-fish, slipped out. This structure was found to be the ectocyst of a hydatid cyst. Although primary hydatid cysts of the pelvis are very rare, the author was unable to find any evidence at the time of the operation of any abnormality in the liver or other abdominal viscera. A radiogram of the chest, taken before her discharge, also showed no abnormality.

Bryan Jeaffreson.

## The Medical Journal of Australia

March 1st, 1941.

*Placenta accreta with complete inversion of the uterus. E. P. Holland.

March 8th, 1941.

Prolapse of a foetal arm and antenatal haemorrhage. M. C. de Garis.

April 19th, 1941.

*Syphilis in pregnant women. E. A. Macknight.

April 26th, 1941.

Case of simultaneous intra-uterine and extra-uterine pregnancy. F. A. Lawes.

### Placenta Accreta with Complete Inversion of the Uterus.

E. P. Holland records the history of a case to which he was called in an emergency on account of post-partum haemorrhage. Delivery had been easy and the placenta was still in the uterus. Bleeding, which had been severe, had stopped, and for this reason the patient was watched for one hour after the birth of the child before removal of the placenta was attempted. Attempts at expression of the placenta brought it down to the vulva entirely attached to the inverted uterus. Treatment of the severe shock of this inversion was unsuccessful, and death occurred shortly afterwards.

Post-mortem examination showed the placenta to be so closely adherent to the uterine wall that there was no line of cleavage. The case appears to have been one of true placenta accreta.

### Syphilis in Pregnant Women.

Ella A. Macknight reports upon the routine examination of pregnant women attending Queen Victoria Hospital, Melbourne, during the periods July 1st, 1932, to November 25th, 1936, and July 1st, 1937, to December 31st, 1940.

Blood was taken for Wassermann's test on the patients' first visit to the antenatal clinic, and when admitted to hospital in labour as an emergency blood was collected from the umbilical cord.

In the first series 9,364 patients gave 96 positive reactions; of these, 18 were probably non-syphilitic and 78 probably syphilitic.

In the second series out of 4,300 cases there were 37 positive reactions; of these, 5 were probably non-syphilitic and 32 syphilitic. This gives a total of 110 probably syphilitic patients out of a total of 13,644 patients examined, or 0.80 per cent. The results of treatment were as follows. In the first series 37 mothers were treated, with 36 live births, and 17 were untreated, with 15 live births. In the second series 26 mothers were treated, with 23 live births, 2 miscarriages and 1 stillbirth; 4 were untreated, with 1 miscarriage, 1 live birth and 2 babies died shortly after birth.

R. H. B. Adamson.

## American Journal of Obstetrics and Gynecology

Vol. xxxix, No. 2.

Presidential Address. James E. King.

The physiology of the anterior pituitary and a note on the medullotrophic hormone. J. B. Collip.

Blood lipoids in pregnancy. Otto H. Schwartz, S. D. Soule, and Bernice Dunie.

Vulvo-vaginal mycoses in pregnancy. Baynard Carter, Claudius P. Jones, R. A. Ross, and Walter L. Thomas.

*Studies on the urinary tract after delivery. W. T. McConnell and Laman A. Gray.

Is there a clinical relation between pyelitis of pregnancy and pre-eclamptic toxaemia? Robert D. Mussey and Sim B. Lovelady.

*Rationale for the use of testosterone propionate in the immediate treatment of excessive uterine bleeding. A. Robert Abarbanel.

Stereoroentgenography of 400 pelves with clinical correlation. John G. Walsh.

Struma ovarii. H. M. N. Wynne, J. S. McCartney, and J. F. McClendon.

Tracheloplasty (Sturmdorf technique) in the treatment of sterility. Oren Moore.

An electric timer as an aid in counting the foetal heart in the second stage of labour and in timing and spacing forceps tractions. Walter B. Mount.

Chemotherapy in obstetrics and gynaecology. R. Gordon Douglas.

Obstetric factors in premature birth. Armand Jean Mauzey.

A study of results in 332 consecutive cases of placenta praevia. Isadore A. Siegel.

A study of 111 cystograms for diagnosis of placenta praevia. Milton A. Carvalho.

*Gärtner's duct lesions of the cervix. Samuel A. Wolfe.

Mesonephroma of the ovary. Howard W. Jones and G. Emory Seegar.

Vaginal use of aluminum hydroxide and colloidal kaolin. S. P. Savitz, L. J. Golub, and H. A. Shelanski.

The use of testosterone propionate in the treatment of the menopausal patient. D. Silberman, H. M. Radman, and A. R. Abarbanel.

Internal endometriosis (adenomyosis) of the urinary bladder. Martin L. Dreyfuss.

Combined extra-uterine and intra-uterine pregnancy. David B. Ludwig.

Simultaneous bilateral tubal pregnancy. Richard Torpin.

Non-traumatic spontaneous rupture of uterus. L. S. Michela, A. J. Blake, and D. E. Zuckerman.

Maternal welfare; what are its fruits? James Knight Quigley.

Society transactions.

Selected abstracts. Abortion.

Vol. xxxix, No. 3.

Reduction of unwarranted operative incidence in obstetrics. S. A. Cosgrove.

*The clinical aspects of pelvic endometriosis. Franklin L. Payne.

Foetal mortality. William A. Scott.

Asphyxia of the foetus and the newborn infant. Stewart H. Clifford.

*The control of cancer in women from the medical viewpoint. Raymond E. Watkins.

The detection of rupture of foetal membranes with the nitrazine indicator. Tom Abe.

Oestrogen and progestin metabolism in pregnant women. G. Van S. Smith and O. Watkins Smith.

*Supravesical extraperitoneal Caesarean section. Edward G. Waters.

Theca cell tumours of the ovary. Malcolm B. Dockerty.

Heart disease and pregnancy. Julius Jensen, Carl Wegner, Edgar H. Keys, Jr., and Hugh R. Smith.

Adrenal cortex in the treatment of nausea and vomiting in pregnancy. J. Kotz and Morton S. Kaufman.

Bilateral ovarian dermoids complicating pregnancy treated by bilateral oöphorectomy. C. J. Andrews, Richard B. Nicholls, and Aurelia Gill Nicholls.

Studies on preservation and use for transfusion of placental blood. Charles S. Fine, Robert L. Alter, and Arthur Baptisti, Jr.

The histological effect of progesterone on hyperplastic endometria. G. Emory Seegar.

The use of the neutral diet and hydration in the treatment of toxaemias of pregnancy. Russell R. de Alvarez.

Acute gonococcal perihepatitis. Walter M. Brunet.

Diagnostic Friedman test in hydatidiform mole and chorion-epithelioma. F. J. Schoeneck.

Parametrial abscess and puerperal septicaemia due to an unusual organism. Melvin L. Stone.

Erythroblastosis foetalis. J. Robert Willson.

Subcutaneous implantation of compressed crystalline theelin pellets in the treatment of menopausal cases. Henry G. Bennett, Gerson Biskind, and Jerome Mark.

The treatment of abnormal menstrual function with oestrogenic and gonadotrophic hormones. Adolph Jacoby and Maurice G. DerBrucke.

Intestinal obstruction as sequel to the Webster-Baldy operation for uterine retroversion. Clarence I. Owen and Frank A. Kelly.

Ovarian pregnancy. J. Clough Frudenfeld and A. N. Webb.

Treatment of cervicitis during pregnancy. Arthur G. King and Roselyn Touff.

Ectopic pregnancy complicated by uterine fibroid. Richard Mandelbaum.

Actinomycosis of the internal female genitalia. Earl L. Hall.

Precocious menstruation. Henry S. Fischer.

Foetal death due to toxaemia of the mother. A. T. Lundgren and William A. Boice.

Some observations regarding the foetal heart tones and the presence of meconium during the course of labour. E. L. King.

The use of antiseptic oil in the treatment of vaginal and cervical infections. W. A. Reed.

A safety labour bed. R. A. Bartholomew.

A membranous cast of the uterus, Fallopian tubes, and cervix. George A. Williams.

Selected abstracts. Stilboestrol and Testosterone.

Vol. xxxix, No. 4.

Limitation of human reproduction. Therapeutic abortion. H. Close Hesseltine, F. L. Adair, and M. W. Boynton.

*A study of the possible significance of the vaginal smear as an additional factor in the diagnosis of incomplete abortion. Paul F. Fletcher.

*The management and treatment of habitual abortion. Ralph E. Campbell and Elmer L. Sevringhaus.

Spontaneous pneumothorax of the newborn infant. Edwin J. DeCosta.

Transverse abdominal incisions in pelvic surgery. G. Wilson Hunter.

Scarlet fever in obstetrics. A. W. Diddle, Ray E. Trussell, and E. D. Plass.

The treatment of bacteriaemias with sulphanilamide. James R. Reinberger.

Granuloma inguinale (granuloma venereum) of the cervix. Rupert E. Arnell and Jesse S. Potekin.

Further studies on the androgen therapy of gynaecological disorders. J. P. Greenhill and S. C. Freed.

Post-partum labial or paravaginal haematomata. Hugh G. Hamilton.

Post-partum sterilization. H. P. Hewitt and J. R. Whitley.

*The induction of labour with small doses of powdered ergot. Claude J. Ehrenberg, Owen F. Robbins, and John A. Haugen.

Intra-uterine death of the foetus after the twenty-eighth week. Henry Buxbaum and Isadore C. Udesky.

*Chronic cervicitis. N. R. Kretzschmar, L. M. Randall, and John Brewer.

Premature infant mortality. Robert M. Grier and Herbert O. Lussky.

Experiences with a placental blood bank. W. Meredith Heyl.

Intermenstrual pain: a surgical condition. Edward F. McLaughlin.

Transperitoneal approach in the management of inaccessible vesico-vaginal fistulae. W. C. Danforth.

Focal infections in pregnancy. Tom D. Paul and Charles Edwin Galloway.

Missed labour. William Pomerance.

Bipartite uterus. E. L. Benjamin and W. C. Danforth.

Full-time pregnancy complicating carcinoma of the cervix. Isidore Daichman and Earle M. Wilder.

Simultaneous extra-uterine and intra-uterine pregnancy. Benjamin Leff and David R. Meranze.

Ovarian pregnancy. Theodore H. Grundfast and Samuel B. Schenck.

A six-year cure of cancer of the vulva in a patient aged 22 years. N. Volney Ludwick.

Society transactions.
Selected abstracts. Endocrinology of pregnancy.

Vol. xxxix. No. 5.

Decidua-like changes in the endometrium without pregnancy. Richard W. TeLinde and Erle Henriksen.
Salt-poor diet and its effect on labour. Ernest E. Wadlow.
*Advanced abdominal pregnancy. Lyman W. Mason.
*Transcervical Caesarean section with peritoneal exclusion and bladder mobilization. Erwin Fletcher Smith.
The advantages of vaginal approach to pelvic pathology. Leonard Averett.
The effects of di-ethyl stilbene (stilboestrol) on menopausal symptoms. John Huberman and M. Jonas Colmer.
Haematometra and haematocolpos following the administration of stilboestrol. A. W. Diddle and W. C. Keetel.
Treatment of senile vulvo-vaginitis with oestrogenic ointment. Daniel R. Mishell and Leon Motyloff.
Caesarean section. Lawrence E. Arnold.
The assay of posterior pituitary extract (pitocin) upon the pregnant human uterus with the Lorand tocograph. Douglas P. Murphy.
Pregnancy and heart disease. Nathan Flaxman.
Vitamin B deficiency as an aetiological factor in pregnancy toxaemias. A. C. Siddall.
The treatment of the immediate post-partum period. M. G. DerBrucke.
Roentgenological survey of chest in pregnant women. Harry J. Perlberg.
Cancer and fibromyomata of the uterus. Don D. Bowers.
Intestinal intubation in gynaecological intestinal complications. Paul M. Glenn and Robert L. Faulkner.
The suboccipitobregmatic circumference. Herbert Thoms and M. S. Godfried.
Plastic reconstruction of the urethra. Samuel H. Geist.
*Regional ileitis as a problem in pelvic diagnosis. Charles A. Gordon and A. H. Rosenthal.
Carcinoma of the cervix in conjunction with pregnancy. S. A. Chalfant and J. H. Mering.
Pregnancies after nephrectomy for tuberculosis. Edmund Lissack.
Masculinizing tumour of the ovary (arrhenoblastoma). S. M. Boltuch.
Krukenberg tumour with involvement of the appendix. Samuel Lubin and Silik H. Polayes.
Carcinoma of the ovary in a child nine years of age. W. Warren Sagar.
Ectopic decidua in the vermiform appendix. Ralph A. Reis and Melvin B. Sinykin.
Carcinoma of the vulva complicating pregnancy. P. B. Russell.
A technique for aspirating viable spermatozoa from the cavity of the uterus as a further study in sperm behaviour. Abner I. Weisman.
Failure of antero-posterior Roentgenographic exposure in multiple pregnancy. Harley E. Anderson.

Late puerperal haemorrhage due to placental polyp. Henry T. Hagstrom.
Prenatal injury of the foetus. Harold A. Schwartz.
Torsion of the uterus. Locke L. Mackenzie and Anna Nimelman.
Spontaneous rupture of papilliferous cyst of the ovary. Maxwell Spring.
Bronchoscopy as an adjunct in the treatment of acute pulmonary oedema complicating eclampsia. Nora D. Dean.
An improved apparatus for treating asphyxia of the newborn infant. Joseph Kreiselman.
A satisfactory cord clamp. John B. Pastore.
Spinelli operation for chronic inversion of the uterus. Gordon F. West.
Inversion of the uterus. E. W. Titus and C. H. Hixson.
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Some sociological and psychological observations on abortion. Virginia C. Hamilton.
Weight changes during pregnancy and puerperium. H. J. Stander and J. B. Pastore.
A clinical study of stilboestrol. M. Edward Davis.
Hyperthyroidism and pregnancy. Carl T. Javert.
*Endometriosis. Roy Fallas and Gordon Rosenblum.
Pseudo-uterus arcuatus and functional malformations of the uterus. Louis Rudolph.
An experiment in cancer control. Catherine Macfarlane, Faith S. Fetterman, and Margaret C. Sturgis.
A study of the incidence of syphilis in pregnant women and some results of therapy. Vince Moseley, J. Lamar Callaway and Jane Stiles Sharpe.
*Results of treatment in carcinoma of the uterine cervix. Roscoe W. Teahan and Hoke Wammock.
The placenta in toxaemia of pregnancy. Benjamin Tenney, Jnr., and Frederick Parker, Jnr.
*Observations on the pathology of trichomonas vaginitis and on vaginal implants with trichomonas vaginalis and trichomonas intestinalis. John F. Kessel and James A. Gafford, Jnr.
Pregnancy and coarctation of the aorta. Curtis L. Mendelson.
Menstrual endometrial biopsy. Lyman W. Mason and William C. Black.
The coexistence of carcinoma and tuberculosis of the uterus. Jacob M. Ravid and Ephraim Scharfman.
An appraisal of the routine use of special post-partum exercise. William B. D. van Auken.
The anaerobic streptococci in tubo-ovarian abscess. W. A. Altemeier.
Blood phosphatase in pregnancy: an indication of twins. J. H. Ebbs and W. A. Scott
Anuria following blood-transfusion. Abraham Bernstein.

The oral administration of stilboestrol. John C. Weed, B. Bernard Weinstein, Frank R. Lock, J. W. Douglas and Conrad G. Collins.

Spontaneous occlusive pyometra. William A. Graham and Samuel D. Failla.

Pregnancy complicated by fibromyomata of the lower uterine segment. Milton G. Potter.

Carcinoma of the cervix in a seven-month-old infant. Edward G. Waters.

Acute anterior poliomyelitis complicating carcinoma of the cervix in a thirty-year-old female. Leo Litter and Hyman Strauss.

Unfavourable sulphanilamide reaction and bleeding duodenal ulcer complicating a puerperium. Goode R. Cheatham.

Friedman tests with ovarian pregnancy. Carl Henry Davis and Verna Stephens-Young.

Haemorrhage in the late puerperium. Herman A. Strauss.

Inversion of the pregnant side of a double uterus. LeRoy E. Bates.

Eclampsia associated with placenta praevia. Frederick A. Wurzbach.

Cancer of the cervix in a virgin with intact hymen. A. F. Lash.

A silver-plated vaginal prosthesis for the construction of an artificial vagina. Buford Word.

An automatic recording apparatus for tubal insufflation. A. Herbert Marbach.

Selected abstracts. Complications of pregnancy.

STUDIES OF THE URINARY TRACT AFTER DELIVERY.

There has always been much controversy on the aetiological factors responsible for pyelitis of pregnancy. In this paper McConnell and Gray enumerate the usual textbook explanations for the dilatation of the ureters and the reasons why pyelitis is more common on the right side. They also quote Hofbauer's work on 14 autopsies in which he found a definite hypertrophy of the peri-ureteral sheath in the lower ureter near the bladder and the theory that atony of the musculature of the urinary tract, brought about by hormonal action, plays the chief part in the cause of the dilatation. The authors have studied the urinary tract in 12 normal cases after delivery to see when the ureters and kidneys get back to normal again. The patients were all primiparae between the ages of 17 and 22 years. An intravenous pyelogram was performed on each case sometime during the last few weeks before delivery and the amount of dilatation of the ureters and pelves of the kidneys were noted. Of these 12 cases, 9 showed a hydronephrosis on the right side and 3 on the left. In 10 cases intravenous pyelograms were made in less than 10 days after delivery. Two of these cases, which had shown moderately large hydronephrosis before delivery, had already returned to normal. In the remaining 8 cases there was a slight reduction in the dilatation in 2, whereas in 2 others there was a very definite increase. Two cases were back to normal on a repeat pyelogram at the eleventh and twelfth weeks; but these had previously had only slight degrees of dilatation. Three cases of more marked dilatation showed no evidence of a return to normal after 7 to 14 weeks. From the study of these 12 normal cases, the

authors came to the conclusion that, while probably most cases return to normal within 8 weeks, some may take much longer than that. They completely disagreed with Lee and Mengert who maintain that the majority return to normal by the ninth post-partum day.

They also studied 28 patients who had had pyelitis of pregnancy from five months to 14 years previously. In 17 the right kidney was apparently solely or mainly involved, 8 were bilateral and 3 were on the left side. The follow-up showed that a right hydronephrosis was present in 20 cases (71 per cent), a left hydronephrosis in 15 patients (53 per cent) and a hydro-ureter on the left side in 10 cases (35 per cent). In 2 patients stones were found in the left kidney. In only 2 patients were apparently normal pyelograms found.

RATIONALE FOR THE USE OF TESTOSTERONE PROPIONATE IN THE IMMEDIATE TREATMENT OF EXCESSIVE UTERINE BLEEDING.

In this paper Abarbanel compares the effects of the administration of testosterone propionate on the endometrium, myometrium, vagina, breast, etc., with the effects of the administration of oestrin and progestin. It is clear that testosterone is not only a powerful androgen but also a very potent gynaecogen. As regards the female, the effects exerted by testosterone may be comparable to those of oestrin and to those of progestin. Its greatest response is on the myometrium. It decreases the rhythmic, intermittent uterine contractions and increases the general contractility of the muscle. The author explains this two-fold effect by stating that it decreases uterine bleeding by causing less blood to flow to the endometrium, through contraction of the myometrium on the smaller blood-vessels, and by abolishing the pumping action of the normal rhythmic contractions.

GARTNER'S DUCT LESIONS OF THE CERVIX.

This duct represents the persisting distal segment of the Wolffian or mesonephric duct. Its persistence *in toto* is rare but small segments of the duct are found in about 20 per cent of all adult females. The cranial end of the duct is usually retained and unites with the proximal collecting tubules of the primitive kidney to form the epoöphoron. Rests in the supravaginal cervix are frequent, especially at the level of the internal os, where the duct enters from the broad ligament and proceeds medially and inferiorly to lie close to the endocervix. When seen microscopically, it presents as a simple tube which gradually widens as it proceeds inferiorly, and in the upper part of the vaginal cervix it produces an ampulla. As it descends the ampulla divides into branches which terminate in gland clusters. The lining of the main duct presents a distinctive lining of low cuboidal or flat epithelium. The cytoplasm is scant and clear and a small round or oval nucleus almost completely fills the cell body.

In this paper Wolfe reports in detail a solitary case containing normal remnants of Gärtner's duct out of a series of 1,413 cervices examined. His explanation for this infrequent occurrence was the fact that the surgical removal of the cervix was performed below the level of the internal os where

the rests are more frequently encountered. He also reports two cases of adenomatoid hyperplasia of Gärtner's duct glands. In one case the posterior fornix contained two small nodules impinged upon the posterior wall of the cervix just above the cervico-vaginal junction. By the description, these were probably areas of endometriosis but, apart from these, an area of hyperplasia of Gärtner's duct remains were found in the upper part of the cervical musculature. In the second case microscopical examination of a polypus revealed that it was composed mainly of smooth muscle fibres, concentrically arranged about large numbers of arterioles and venules. About the middle of the polyp, but limited to only one of its surfaces, the muscle zone presented collections of proliferating glands which encroached upon the endometrial lining. These glands were arranged radially about wider duct branches. They were lined by flat or low cuboidal epithelial cells. In the author's opinion, the polypus was a small submucous fibroid clothed by endometrium with remnants of Gärtner's duct glands in the muscular zone near the mucosa. Although the author has had no experience of a malignant Gärtner's duct tumour of the cervix, such cases have rarely been described. A true adenoma of these remnants was discovered in some nodules situated behind the cervix on microscopical examination. The removal was incomplete and two years later a further extension of the mass, involving the entire posterior aspect of the cervix, was found. Further biopsy and treatment were refused.

THE CLINICAL ASPECTS OF PELVIC ENDOMETRIOSIS.

A great deal has been written about this interesting gynaecological condition but few papers stress the importance of the physical signs and symptoms which are used for the purpose of diagnosis. In this paper, Payne found that 64 per cent of the major lesions of endometriosis were located in one or both ovaries and 25 per cent in the pouch of Douglas. He found that the characteristic feature of endometriosis was its common association with other pelvic pathology which overshadowed both the symptoms and the physical signs of the ectopic endometrium. These lesions were mainly fibroids and inflammations and these, with other rarer ones, occurred in 81 per cent of the cases. The great majority of cases occurred between the ages of 30 and 50, the youngest patient being 18 years old and the oldest 62. The chief symptom was some alteration in the menstrual period, especially that of menorrhagia, and severe dysmenorrhoea occurred in 35 per cent. However, some form of pain, either backache or lower abdominal pain, occurred in most cases and this pain tended to be aggravated at the time of the menstrual periods. Sterility and dyspareunia were the chief symptoms in six per cent but it was found that 40 per cent of the married women had not had any pregnancies. As these symptoms tended to be masked by the symptoms and signs of the associated lesions, only 36 per cent were correctly diagnosed.

Since ovarian endometriomata are removable, the author advises surgical treatment. In this series, bilateral oöphorectomy was necessary in 51 per cent and in 49 per cent it was possible to conserve one ovary and often the uterus. In young women cauterization of transplants in the better ovary

was performed, so as to save some menstrual and procreative function. Of the 47 patients with endometriosis of the recto-vaginal septum, three-fourths were treated surgically and one-fourth by irradiation. In all cases of this disease the treatment, whether radical or not, or whether surgical or by irradiation, depended upon the severity of the symptoms, the patient's age, and upon whether the major lesions could be removed.

THE CONTROL OF CANCER IN WOMEN FROM THE MEDICAL VIEWPOINT.

As cancer develops in locations subjected to repeated injury or at the site of chronic inflammatory lesions, Watkins stresses the importance of eradicating all known predisposing lesions, of detecting the cancer early, of prompt and efficient management as soon as possible, and of cancer education of the public.

With regard to cancer of the cervix, he quotes Groves, who found that only two women in 6,000 who had cervical repairs performed later developed cancer in this area. He also quotes the value of periodic examination in the control of cancer and that this will be appreciated more as time goes on. The early diagnosis of gynaecological cancer is the doctor's responsibility and he stresses the important part that has to be played by the general practitioner, who must see that an immediate investigation is carried out on the slightest suspicion of malignancy. Seventy per cent of the 154 patients with cervical cancer seen in the author's clinic since 1930 showed the carcinoma to have spread definitely beyond the confines of the cervix.

As it is thought by Hinselmann, Schiller and others that beginning carcinomata have the appearance of leucoplakia before they can be recognized grossly, the colposcope and Gram's iodine stain were devised for the detection of such lesions. Because of considerable variation in thought as to the practicability and value of these tests, the author obtained the opinion of 11 teachers pre-eminent in the field of gynaecological cancer. All had had experience with the Schiller test. Nine had found none or very few cases of malignancy by this means. One found four early cancers without gross evidence of the disease in 184 consecutive cases; three of these gave a positive test and the other one did not; he stated that he removes a cone of tissue whenever he gets a positive test and that only five per cent of these positive cases proved to be cancerous. One well-known worker in cervical cancer answered that he had not picked up a single instance of cervical cancer with the Schiller test. As so many important men have been unable to duplicate Schiller's findings of so many early superficial carcinomata, it makes one wonder if actual cancer was present in the 51 patients in whom Schiller reported a 96 per cent five-year survival.

Regarding the use and value of the colposcope, only two of the 11 considered this instrument of enough value to use routinely. They all agreed that excision and biopsy of leucoplakic patches was the correct procedure but most stated that they had seen but few such lesions.

Watkins reports that the majority of the women in his clinic with uterine cancer were seen for the first time in an advanced stage. He attributes this

delay mainly to the fact that women are accustomed to vaginal discharges, that it is customary for them to ascribe such symptoms to the change of life and that they seek advice from older women who comfort them by saying that they experienced similar symptoms at this time of life. As the doctor has but little chance to help unless the patient presents herself when the disease is in an early stage, the author strongly advocates the widest education of women as to the significance of abnormal menstruation and vaginal discharges.

SUPRAVESICAL EXTRAPERITONEAL CAESAREAN SECTION.

Although the lower segment transperitoneal operation is used for potentially septic cases with good results, many obstetric surgeons are loath to open the peritoneal cavity in frankly septic cases even if the child is still alive. In this paper, Waters describes in detail an extraperitoneal operation which he describes as supravesical. The essential step of this operation is the stripping of the endopelvic fascia, which covers all the sides of the bladder, together with its peritoneal covering, from off the top of this viscus. This fascial plane has to be incised again behind the bladder before the bladder can be pushed downwards behind the pubis and the front of the lower uterine segment exposed. The area of uterine muscle exposed for incision is a large one and an extra large baby can thus be delivered without risk of injuring such important structures as the ureters or uterine arteries.

Waters considers that it is an easier operation to perform than that by the Latzko technique and that there is much more room through which the baby can be delivered. As the Latzko operation opens up easily infected cellular tissue at the side of the bladder, this operation advocated by Waters is a great advance on the older technique. He reports the results of 32 operations. There was no maternal death and only one foetal death. The operation took about 60 minutes to complete on the first two occasions but the average time for the remainder was 38.5 minutes. In the earlier experiences the peritoneal cavity was inadvertently opened six times before the uterus was incised, and immediately repaired. In the discussion which followed the reading of this paper, many important surgeons were impressed with the possibilities of the operation.

A STUDY OF THE POSSIBLE SIGNIFICANCE OF THE VAGINAL SMEAR AS AN ADDITIONAL FACTOR IN THE DIAGNOSIS OF INCOMPLETE ABORTION.

After reviewing the literature concerning the uses of the vaginal smear in clinical diagnosis, the author quotes the work of Papanicolaou and Kelly who observed certain well-marked changes in the consistence and make-up of the smear in pregnancy. Soon after the beginning of pregnancy there is a distinct tendency for the cells to assume certain characteristic forms. This change is characterized by an excessive increase in the number of cells much larger than is found in the non-pregnant state or even in the premenstrual phase of the human cycle. After the onset of parturition degenerative changes set in and result in an extensive desquamation of all cellular excess;

at this stage pavement cells from the outer basal zone, as described by Smith, abound in the smear. When such cells are found in a case of suspected termination of an early pregnancy, the author is of the opinion that it might be accepted as a feature diagnostic of this condition.

Although his series of cases of incomplete abortion was relatively small, the author found the following changes were regular and consistent in almost every smear studied. Superficial and intra-epithelial cells were present in relatively small numbers and were about normal in size. The outer basal or pavement cells were present in sufficient numbers to cause them to be easily recognized as characteristic of the incomplete abortion smear. They were equally as numerous as, or more numerous than, the superficial cells. Their nuclei were large in proportion to the cytoplasm, more so than is observed in the superficial cells in pregnancy smears, and there was not so marked a contrast with the cytoplasm as in the superficial cells. The inner basal or germinative cells were also consistently present in the smears of incomplete abortion. They were smaller and more consistently round or oval in shape than the outer basal cells. The author describes his technique for obtaining and staining the smear.

THE MANAGEMENT AND TREATMENT OF HABITUAL ABORTION.

In a short article Campbell and Sevringhaus describe their experience of treating 13 cases of habitual abortion. Each patient had aborted twice or more and only one had had a mature living child. All of these cases were treated with corpus luteum extract, usually in the form of progesterone. The dosage given varied considerably, especially in the first few cases of this series. However, the authors are of the opinion that a safe dose is two rabbit units weekly. Of these 13 cases, 11 went to term and had spontaneous deliveries. One patient aborted at the fourth month and the other at the sixth month.

THE INDUCTION OF LABOUR WITH SMALL DOSES OF POWDERED ERGOT.

In 1935 the authors experienced a dramatic maternal and foetal death ten hours after the first ingestion of three 5-gr. doses of quinine sulphate and they came to the conclusion that death was due to quinine poisoning. Consequently, they experimented with a dried ergot preparation and they found that small doses can be tolerated by pregnant women without ill effects. Their technique for the induction of labour was to give one to two ounces of castor oil half an hour before the first dose of ergot. Beginning with smaller amounts, it was determined that a dose equivalent to 12 gr. (0.8 grm.) U.S.P. ergota preparata, administered by mouth at intervals of from two to three hours, was effective for inducing labour. One hundred and forty-two cases were dealt with on these lines and 78.2 per cent were successful 39 days before to 24 days after term. In a small group of 25 cases, posterior pituitary extract was given as well as the ergot and castor oil; 68.0 per cent were successful in cases 8 days before to 17 days after term. In another small group of 20 cases, artificial rupture of the membranes was performed either

before or after the administration of ergot; the longest latent period in two cases was 24 hours. There was no maternal death and only three cases of foetal death; two of which were due to very difficult deliveries and one was dead *in utero* before the first dose of ergot.

### Chronic Cervicitis.

The Committee of Clinical Affairs of the Central Association of Obstetricians and Gynaecologists sent out a questionnaire on chronic cervicitis to all the members of the Association. The general consensus of opinion was that chronic cervicitis is a lesion of considerable importance in relation to body functions outside the pelvic viscera, as well as being the cause of significant changes in the pelvis. Opinion indicated that birth trauma was considered by far the most important causal factor and that most thought that the Schiller test and the colposcope added little to the investigation of this condition. About 36 per cent of the opinions were not impressed with the view that chronic cervicitis may be the cause of dysmenorrhoea, dyspareunia or of urinary symptoms but practically all agreed that it may be the cause of pelvic pain, backache and sterility. Thirty-nine per cent did not think that it was an important aetiologic factor in cancer and 78 per cent considered that it was important as a focus of infection.

The commonest form of treatment used was the actual cautery; the next in order of frequency was the Sturmdorf's amputation, trachelorrhaphy and conisation. The number of complications (685) following treatment was unusually high. Of these, 40 per cent occurred after the use of cautery. Haemorrhage (259), stenosis of the cervix (208) and upper genital tract infection (148) were, by far, the commonest of these complications and in this order of frequency. Cauterization accounted for 35 per cent of infection, 38 per cent of haemorrhage and 54 per cent of stenosis on analysis of these three important complications. It was surprising to find that Sturmdorf's amputation was followed by a certain number of examples of haemorrhage and stenosis of the cervix. The Committee is of the opinion that the large number of complications reported should prompt the Profession to improve the methods of diagnosis and treatment of this very common condition.

### Advanced Abdominal Pregnancy.

Basing his experience on 3 cases of secondary abdominal pregnancy, the author enumerates certain points which should be used in establishing the diagnosis of this unusual condition. He says that there is usually a history of symptoms of an early ectopic pregnancy with probable tubal abortion. Later, the foetal movements become unusually noticeable by the mother, and the foetus can be palpated with great ease. The cervix remains firm and is frequently displaced to one side of the mid-line, and possibly forwards as well. The uterus itself may be palpable and is usually mistaken for a fibroid or an ovarian cyst. At the end, there is frequently the onset of some abdominal pain which coincides with the cessation of foetal movements. In a review of 69 cases, including 3 of his own, the

author reports a mortality of 18.8 per cent. This is about the average rate for any series so far published. The author analyses the cause of death. Seventy-five per cent of the recoveries occurred in cases in which the placenta was easily removed, or when no attempt was made to remove the placenta. There was no death when the placenta was left *in situ* and the abdomen was closed without drainage; whereas a rate of 22.7 per cent occurred when marsupialisation or drainage was instituted after leaving the placenta alone. Similarly, in cases in which the placenta could easily be removed, the mortality was considerably increased by packing or drainage. These considerations alone seem to stress the importance of closing the abdomen completely, however the placenta is treated. The author is of the opinion that, as necrosis of the placenta and of the membranes is a physiological process, this organ should be left *in situ*, unless there is a certainty that haemorrhage from the vessels to the placenta can be controlled by ligature at the time of the removal.

TRANSCERVICAL CAESAREAN SECTION WITH PERITONEAL EXCLUSION AND BLADDER MOBILIZATION.

As it is quite evident that the lower uterine segment operation provides a wider margin of safety than the classical methods, Smith advocates that all obstetricians should be able to perform this operation, and should learn the various techniques which might be applied to certain cases. The case which calls for variation of technique is the infected case, in which a living child can be delivered by section, and the author advocates a transperitoneal operation with obliteration of the general peritoneal cavity by suture from the area of uterine incision. He approaches the lower segment by Pfannenstiel's incision through the anterior abdominal wall, cutting the parietal peritoneum transversely directly above the bladder. After recognizing the lower edge of the vesico-uterine peritoneal pouch, the visceral peritoneum is cut transversely, keeping as close to the edge of the bladder as possible. The bladder is completely separated from the cervix, the bridge of peritoneum at the lateral edge of the bladder is divided on each side and the superior parietal peritoneum is stitched to the visceral peritoneum from one side to the other. After incision of the lower segment, the delivery of the foetus and placenta, and the suture of the muscle incision, the sutured peritoneal flap is brought down over the cervical incision and attached to the posterior edge of the vesical peritoneum. The anterior edge of the vesical peritoneum is brought upwards and sutured high on the peritoneal wall, thus forming a double flap of peritoneum covering the incision.

REGIONAL ILEITIS AS A PROBLEM IN PELVIC DIAGNOSIS.

Regional ileitis has only been recognized as a pathological and a clinical condition during the last few years and, as it is situated in the ileum close to its termination, the mass which is palpable must often enter into the differential diagnosis of more common gynaecological conditions. It

may be found so low in the region of the right vaginal fornix, and so close to the uterus that it may be mistaken for an adnexal lesion.

The authors stress the importance of always bearing this condition in mind, and of noting the symptoms, so that it can be recognized and diagnosed. They also maintain that every gynaecological surgeon should be competent to carry out the correct operative measures, whenever he finds this lesion, on exploring the pelvic cavity.

Crohn described the condition in 1932 as a subacute or chronic granulomatous process, finally causing stenosis of the lumen of the intestine, and associated with a palpable lower abdominal mass with, later on, multiple fistulae. The most constant symptoms are loss of weight, abdominal pain, and diarrhoea associated with an abdominal mass. The loss of weight is due to fear of eating, rather than the disease, since abdominal pain and cramps quickly follow ingestion of food. The diagnosis is established by X-rays, but since the caecum and colon are rarely involved it is necessary to give a barium meal rather than a barium enema. Resection, well beyond the involved area, is indicated, as a short circuit operation does not arrest the disease and fistulae will follow. The authors advise a two-stage operation.

ENDOMETRIOSIS.

Fallas and Rosenblum report a series of 260 private hospital cases which had been treated for endometriosis. The case histories or the description of operative findings were not as full as they would have liked but they have been able to collect some useful data. While reviewing the literature on this subject, the authors were impressed by the large percentage of failures to make a pre-operative diagnosis, and by the lack of standardization in the treatment of this condition. Also, in their own experience, they found that too often, among general practitioners and general surgeons, there was a failure to make the diagnosis even with the abdomen opened and consequently there was a failure to apply proper or adequate treatment.

These 260 cases were collected during a period of 9 years, and they represent 1.62 per cent of all gynaecological laparotomies performed in the same period of time. The internal type (adenomyoma) tended to occur rather later in life than the external or pelvic type. The uterus (44.8 per cent), ovaries (23.2 per cent) and peritoneum (14.2 per cent) were easily the commonest situations of involvement and there was a great tendency for endometriosis to be associated with other pelvic pathology. Fibromyomata of the uterus occurred in 41.5 per cent of the cases and chronic pelvic inflammatory disease in 17.3 per cent. Dysmenorrhoea was the predominant complaint in this series and was noted in 43.4 per cent of cases. It was a more constant symptom in the general pelvic type than in the uterine type. Menorrhagia was complained of in 47.7 per cent, and it was most noticeable in the internal or uterine type. Retroversion of the uterus was present in over half of the cases in which the position had been noted.

After considering the treatment carried out on exploring the pelvic cavity, the authors come to the conclusion that in external endometriosis the relief of symptoms was decidedly better when all ovarian tissue was removed than when some was conserved. They think that this radical treatment should be carried out in all cases about and beyond 40 years of age, and should be seriously considered even in the younger patients. The internal type was adequately dealt with by removal of the uterus.

RESULTS OF TREATMENT IN CARCINOMA OF THE UTERINE CERVIX.

In spite of the fact that the cervix is accessible for diagnosis and treatment, and that this region tolerates radiation well, the results obtained in the treatment of cervical cancer are poor. The authors are of the opinion that this is mainly due to the extent of the disease when treatment is started. An analysis of the time interval in 167 cases in which notes were complete showed that there was an average of 5.55 months from the onset of symptoms to the time of the first visit. This interval was gradually decreasing but an average interval of two months was still being maintained between the first visit and the first pelvic examination. They also found that there was an average delay of 3½ months from the time of the first examination to the time of the first treatment. They thought that this was due to incorrect diagnosis, disbelief on the part of the doctor that cancer is curable, and the unwillingness of the patient to submit promptly to the necessary treatment. The authors advocate a thorough clinical examination in all cases. This includes an X-ray examination of the lungs, lumbar spines and pelvis as a routine, a careful bimanual examination under anaesthesia *via* the vagina and the rectum, the dilatation of the cervix to exclude the presence of a pyometra, and a cystoscopic examination for evidence of involvement of the bladder wall. This is done on every case and if there is any suggestion of ureteral blocking, on examination or in the history, the ureters are catheterized as well. Nearly 60 per cent of cases were found to be in stage 4 and 31 per cent in stage 3, leaving less than 10 per cent in stages 1 and 2.

All cases were treated exclusively by radiation. Prior to 1933, 72 cases were treated with radium after Heyman's method of small doses repeated once or twice to give a total of 6,600 radium milligram-hours. This was followed by a course of deep X-ray therapy which was given 3 times a week for a total of 2,400 r. units to each of four ports. Since the beginning of 1933 49 cases were treated by the same course of X-rays and, immediately on completion of this course, by radium; 8,000 milligram-hours of radium was given in one dose; 33.33 mg. were inserted into the uterine cavity and cervical canal, and a similar amount was arranged in the vagina. This necessitated leaving the radium *in situ* for nearly 5 days. They obtained a 19.4 5-year cure rate by the old method and a 22.4 rate by the newer method. The authors are convinced that, except for the extent of the disease, the initial treatment is the most important factor in determining the ultimate result.

OBSERVATIONS ON THE PATHOLOGY OF TRICHOMONAS VAGINITIS AND ON VAGINAL IMPLANTS WITH TRICHOMONAS VAGINALIS AND TRICHOMONAS INTESTINALIS.

There is still a great deal which is not fully understood with regard to trichomonas infection of the vagina. In this paper the authors have made a useful contribution towards solving many of the problems which are controversial. Three theories are held concerning the aetiology of this disease, (*a*) that the trichomonas vaginalis is the primary agent, (*b*) that the trichomonas is a parasite which multiplies rapidly in the suitable environment which is produced by some bacterium or other aetiological agent, and (*c*) that the trichomonas and some bacterium may both be responsible, one producing the initial tissue changes necessary and the other being a secondary invader. The authors are of the opinion that some factor, in addition to the trichomonas, probably plays a role in the production of the clinical vaginitis. They base their view on histological investigation of the vaginal mucosa, and on transmission experiments. They found that areas of the surface mucosa were covered with coagulated material in which trichomonas, leucocytes and red blood-cells were commonly found. The surface epithelium was usually intact but in certain areas showed erosion with the migration of flagellates between the surface cells. In the sub-epithelial layers, areas of intense infiltration were found but no flagellates. In some instances definite necrosis appeared within these areas. In these necrotic patches the trichomonas were commonly found. Thus the authors conclude that the vaginitis is not brought about by simple invasion of the flagellates from the lumen of the vagina, but that there is some additional mechanism, either toxic or bacterial in nature, which is responsible for the primary tissue changes. Implants into normal vaginae of exudate from characteristic vaginitis cases, which contained T. vaginalis and bacteria, resulted in all instances in the occurrence of characteristic symptoms and in the recovery of the flagellates. Implants of cultures of T. vaginalis and bacteria produced only one case of typical vaginitis, and implants of the bacteria alone produced only a mild vaginitis without characteristic discharge. The question whether T. vaginalis is a species distinct from T. intestinalis was also studied. The authors came to the conclusion that it is distinct. This opinion was based on the fact that it was impossible to cause a vaginitis in humans or in monkeys with experimental implants of trichomonas intestinalis.

BRYAN JEAFFRESON.

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## The Journal of the American Medical Association

Vol. cxv, No. 14, October 5th, 1940.

*Reduction of elevated blood-pressure by the administration of renal extracts. A. Grollmann, J. R. Williams, and T. R. Harrison.
*Human serum transfusions. S. Levinson, F. Rubovitz, and H. Necheles.

Vol. cxv, No. 15, October 12th, 1940.

*Pregnandiol excretion following bilateral oöphorectomy in early pregnancy. G. Seegar and E. Deles.

Vol. cxv, No. 16, October 19th, 1940.

*Should solution of posterior pituitary be used in labour? J. Sharkey.
*Abuse of solution of posterior pituitary during early labour. G. Pendleton.
*The use of posterior pituitary in modern obstetrics. J. B. De Lee.

Vol. cxv, No. 17, October 26th, 1940.

*Sterility in the male. H. Kreutzmann.
*The nature of human infertility. S. Meaker and S. Vose.
*Veratrum viride in the treatment of eclampsia. R. Bryant and J. Fleming.
*Sulphathiazole. G. Carroll, L. Kappel, and B. Lewis.

Vol. cxv, No. 20, November 16th, 1940.

*Intramedullary (sternal) transfusion of human bone marrow. M. Morrison and A. A. Samwick.

Vol. cxv, No. 23, December 7th, 1940.

*Relation of anterior lobe of the hypophysis to other endocrine glands. P. E. Smith.
*Relations of anterior lobe to carbohydrate and fat metabolism.

Vol. cxv, No. 25, December 21st, 1940.

*The anterior lobe of the hypophysis in intermediary metabolism.

Vol. cxv, No. 26, December 28th, 1940.

*Stilboestrol-induced gynaecomastia in the male. C. W. Dunn.
*Alleged hepatotoxic action of stilboestrol. S. Freed, E. Rosenbaum, and S. Soskin.
*Clinical studies on stilboestrol. E. von Haam, M. Hammell, T. Rardin, and R. Schoene.
*Lactogenic and mammogenic hormones. O. Riddle.
*The antihormones. D. Thomson, J. B. Collip, and H. Selze.

Vol. cxvi, No. 3, January 18th, 1941.

*Dysfunctions of the anterior lobe of the pituitary. E. Sevringhaus.

Vol. cxvi, No. 4, January 25th, 1941.

*Chemotherapy of gonococcal infections. Van Slyke, R. R. Wolcott, and J. F. Mahoney.

*Pharmacology of sulphapyridine and sulphathiazole. S. Lichtman and W. Bierman.

*Agranulocytosis from sulphathiazole. P. Kennedy and M. Finland.

REDUCTION OF ELEVATED BLOOD-PRESSURE BY THE ADMINISTRATION OF RENAL EXTRACTS.

The authors confirmed, by experiments in rats and dogs, that renal extracts do lower the blood-pressure in animals with experimental renal hypertension. A small number of patients were then treated by administration of the renal antipressor substance and in most of them a decline in the blood-pressure was noted. The authors, however, consider the results were inconclusive because the effect of suggestion could not be excluded, because there is no certain way of determining in which patients the hypertension is exclusively renal in origin, and finally, because severe reactions have occasionally been observed in animals. They give a table showing and comparing the effects of their renal antipressor substance with other depressor substances.

HUMAN SERUM TRANSFUSIONS.

The authors describe a series of 47 patients suffering from various conditions in which human serum transfusions were given. The results were good, and no reactions were observed, though the authors state great care is needed in the preparation of serum if reactions are to be avoided. They claim as advantages of serum over blood-plasma the greater time serum can be preserved, the absence of sodium citrate and of fibrin precipitates, and that no preliminary typing and compatibility tests are required.

PREGNANDIOL EXCRETION FOLLOWING BILATERAL OÖPHORECTOMY IN EARLY PREGNANCY.

The authors report a case in which a continuous series of pregnandiol determinations were made throughout a normal pregnancy in which both ovaries were completely removed on the 63rd day. There was no disturbance or any other abnormality of the pregnancy, which continued normally to term. The excretion of pregnandiol remained far below that found in a normal pregnancy and only on two occasions did it even slightly exceed the values found in non-pregnant menstruating women. Cyonin and chorionic gonadotropin determinations gave values comparable to those found in normal pregnancies.

SHOULD SOLUTION OF POSTERIOR PITUITARY BE USED IN LABOUR?
ABUSE OF SOLUTION OF POSTERIOR PITUITARY DURING EARLY LABOUR.
THE USE OF POSTERIOR PITUITARY IN MODERN OBSTETRICS.

These three papers dealing with the use of posterior pituitary extracts in labour were read before the Section of Obstetrics of the American Medical Association. Though in none of the papers is any new material presented all the authors weigh the uses and still more the abuses of the drug in childbirth.

Sharkey concludes that the use of posterior pituitary in normal labour to hasten delivery is to be condemned. It may be used with care: (*a*) In certain cases of true primary uterine inertia, provided no mechanical hindrance to delivery is present. (*b*) In lieu of low forceps when the second stage is long because of weak pains and there are no facilities for forceps delivery. (*c*) In abruptio placentae by those with sound obstetrical judgment.

The dose should never exceed 3 minims (0.18 c.c.) and is preferably 1 minim with an interval of at least 30 minutes between the doses.

Pendleton does not favour the use of pituitary extract at all in labour. He found the stillbirth and neonatal death rates much increased and a higher incidence of cases needing either version or manual removal of the placenta. He found quinine equally as dangerous as pituitrin.

De Lee's paper, while considering and giving full weight to the dangers of the drug, discusses the conditions under which he considers it may be used with profit. It is useful in abortion to hasten expulsion of the foetus and to conserve blood. It may be injected directly into the cervical wall during curettage for incomplete abortion.

Pituitrin is useful to start labour except in cases of placenta praevia. The nasal method is dangerous and some women react too strongly to even very small doses no matter by what method it is given. De Lee gives one half unit and watches the effect with an ether can in hand. At the end of 20 minutes 1 unit is given and thereafter a like dose every 20 to 30 minutes until some effect is seen. If the contractions then die off the course is repeated. He finds pitocin raises the blood-pressure just as much as the total extract. In the second stage the indications for the use of pituitrin are well defined and defensible. In the third stage the advantages of a speedier separation of the placenta obtained in many cases are offset by the frequent call for manual removal. For post-partum haemorrhage the posterior pituitary extracts are being replaced more and more by ergot derivatives.

STERILITY IN THE MALE.

Cases of male sterility can be divided into two groups, urological and endocrinological. Some urological cases are congenital, hypospadias, crypt-

orchidism and abnormal attachment of the epididymis to the testis, but most are due to an old gonorrhoea leading to stenosis of the ducts.

In cases of aspermia in which testicular atrophy is not present there must be some occlusion. To determine whether the vas is patent the author inserts a catheter into the bladder and then injects 5 per cent of silver proteinate into one vas and 2 per cent of mercurochrome into the other. Attempts to relieve fibrous strictures of the vas have not been successful in the author's hands. When the vasa are patent aspermia is due to obstruction in the epididymis. For this he recommends Hagner's operation for anastomosing the vas to the vasa efferentia of the globus major. Chronic seminal vesiculitis may impair sperm motility and may be treated by massage and heat. Chronic prostatitis is not considered a common cause of sterility.

If urological lesions are excluded one must presume some endocrine disturbance. These can be diagnosed by examination of the semen, the three factors to be considered being the number of spermatozoa per c.c., the percentage of abnormal forms, and the degree of motility. He quotes Hotchkiss's work to the effect that lower numbers are compatible with fertility than was formerly supposed, men with counts as low as 2,250,000 per c.c. being fertile.

As regards abnormal forms, in 48 men observed over a period of years 35 per cent had less than 20 per cent of abnormal forms; pregnancy occurred in every case.

He divides all patients with abnormal semen into four groups as follows:

1. Normal count, normal percentage of normal forms, lowered basal metabolic rate.

2. Oligospermia and a normal percentage of healthy sperm.

3. Normal count with an increase of abnormal forms.

4. Oligospermia with an increase of abnormal forms.

All the patients in group 1 responded to thyroid, but in the other groups failure usually followed all forms of endocrine therapy. While testosterone propionate can increase the number of sperms, provided small doses are used, this effect is not constant and in two of the author's patients this drug led to an increase in the percentage of abnormal forms. If drugs of this type are to be used then they should be controlled by repeated sperm analyses.

THE NATURE OF HUMAN INFERTILITY.

This is a very general review of the problem of human infertility. In the authors' opinion most cases are due to multiple causes. In 200 consecutive cases there were at least two conditions capable of depressing fertility present in each case. The average number of causative factors present was

4.8 per case. Most of the causes of infertility are due directly or indirectly to environmental factors, and in particular to the artificial conditions of civilized life. In a small proportion of cases there is also a hereditary tendency to low fertility.

### Veratrum Viride in the Treatment of Eclampsia.

In a series of 120 consecutive cases of eclampsia the gross maternal mortality rate was 1.67 per cent. This low rate was attributed to the employment of veratrum viride dehydration with dextrose of magnesium sulphate, an increased fluid intake and the withholding of sedatives. Only the simplest methods of inducing labour were used. None of the patients died of the immediate eclampsia, the two deaths being due to infection on the 14th and the 65th days of the puerperium respectively.

The blood-pressure falls very rapidly after giving veratrum, sometimes as low as 50 mms. systolic. This immediate fall is followed by a more prolonged period in which the pressure remains well below the original pressure. Vomiting is an early effect and is often severe. Individual susceptibility is marked and no absolute standardization of the dose is advisable. A typical course of treatment given by the authors is as follows:

1. Ten minims of veratrum are repeated every 10 to 15 minutes till the pulse-rate is below 60, or the systolic blood-pressure is below 120; thereafter till consciousness returns the drug is repeated in doses of 3 to 10 minims, if the pulse-rate is over 80 or the systolic blood-pressure over 150. After the patient is conscious the dose is repeated in the presence of pre-eclamptic symptoms.

2. Ten c.c. of 50 per cent magnesium sulphate solution are given intramuscularly followed by 5 c.c. every 6 hours for 4 doses and then 5 c.c. every 12 hours for 4 doses.

3. Five hundred c.c. of 20 per cent dextrose are given intravenously, and repeated every 6 to 10 hours till consciousness returns.

4. The bladder is catheterized and an enema is given.

5. The pulse-rate and the blood-pressure are checked hourly during coma and thereafter every 2 hours.

6. Fluids by mouth are forced.

7. No sedatives, except for extreme restlessness or labour, are given.

8. A salt-free diet is ordered as soon as tolerated.

9. No attempt is made at isolation.

10. For labour pains rectal paraldehyde is used.

### Sulphathiazole.

Absorption of thiazole compounds is much more variable than that of sulphanilamide or sulphapyridine. The peak of blood concentration

occurs in about 4 hours after administration. As much as 14 grm. can be given daily with no ill effects. One woman was given 1 grm., dissolved in 200 c.c. of water, intravenously together with 6 grm. orally within 24 hours. A blood concentration of 17 mgm. per 100 c.c. was obtained without ill effects. It is essential to give the drug in adequate dosage and for a week after all clinical evidences of the disease have cleared up.

Reactions are common and in a considerable number of cases the drug had to be discontinued. Pain in the abdomen, nausea, vomiting, headache, melancholia, diarrhoea, and nervousness have been the chief complaints. A peculiar conjunctivitis, unique for this drug, has been noted. Anuria or oliguria may occur and be associated with concretions of the drug. Like those formed by sulphapyridine these calculi are not opaque to X-rays.

### Intramedullary (Sternal) Transfusion of Human Bone Marrow.

The patient was suffering from an aplastic anaemia with marked anaemia, granulocytopenia, thrombocytopenia and an absolute lymphocytopenia. No cause for the condition could be found.

Following a direct blood-transfusion of 500 c.c. he was given 3 intrasternal injections of 3, 5 and 5 c.c. of bone marrow obtained by sternal puncture from the patient's brother. The condition of the patient improved.

The authors claim that there may be an unknown factor present in normal marrow which, when thus injected, may stimulate the maturation of haematopoietic constituents already present in the diseased marrow. There are no technical difficulties in doing the intrasternal injection.

### Relation of Anterior Lobe of the Hypophysis to other Endocrine Glands.

This is the first of a series of articles on glandular physiology and therapy intended to provide a comprehensive summary of recent developments. The first series was published 15 years ago, and since then there have been two others at five-year periods.

Since the last article published in 1935 Fisker does not consider any essentially new relations have been revealed between the hypophysis and the other glands of internal secretion, nor have any of the established views been shown to be erroneous. The most important advance in recent years has been the demonstration of the interrelation between the pituitary and the adrenal cortex in the metabolism of fats and carbohydrates. Advances in the purification of the various pituitary preparations have been slow because of their protein character. Aside from the so-called metabolic principles, five principles continue to be generally recognized as coming from the anterior lobe. These are: (1) The growth (somato-

tropic) principle. (2) The gonadotropic hormone or complex. (3) The thyrotropic hormone. (4) The corticotropic (adrenatropic) hormone. (5) The lactogenic hormone.

The effects of hypophysectomy are reviewed. They have been studied in all common laboratory animals and the picture is quite uniform. Survival for considerable periods is possible and depends on care in maintaining a normal food intake and a normal temperature. In monkeys as little as one-fourth of the gland will prevent the development of the disabilities.

(1) *The growth principle.* In view of the complex factors involved in the process of growth, and also because other hormones, prolactin for instance, can control growth, doubt has been thrown on the existence of a specific growth principle. In view of the fact that contamination of extracts of the growth factor with other anterior pituitary factors can be greatly reduced without impairing the growth-stimulating property of the extracts it would appear that there does exist a specific principle stimulating epiphysial cartilages.

(2) *Gonadotropic complex.* The present consensus of opinion is that there are two gonadotropic hormones. Little is known of their chemical composition. The luteinizing hormone is not identical with the gonadotropic principle of human pregnancy urine.

(3) *Thyrotropic hormone.* The injection of this extract into responsive species results in most of the thyroid changes characteristic of exophthalmic goitre.

(4) *The corticotropic hormone.* There has been much question as to whether the cortex-stimulating action of the hypophysis was due to a distinct hormone, but the evidence supplied by Collip, Moon and others shows that it is distinct, and has no other action than that of stimulating the adrenal cortex. It can restore the work capacity of hypophysectomized animals. It seems probable that the enlargement of the adrenals in normal animals under conditions of stress is due to liberation of unusual amounts of corticotropic hormone by the hypophysis.

(5) *The lactogenic hormone.* The pituitary lactogenic hormone is purely a secretogogue and does not cause development of the breasts. It is the only pituitary hormone that has been secured in crystalline form. The injection of prolactin gives but a temporary increase in milk production in cows, and clinical studies show little or no response following its injection in man.

### Relations of Anterior Lobe to Carbohydrate and Fat Metabolism.

This is a very complex subject. Its important aspects seem to be as follows:

(1) The greatly increased sensitivity to insulin of hypophysectomized animals, shown by Houssay and Potick to be due to loss of the anterior

lobe only. (2) The amelioration of experimentally produced diabetes by hypophysectomy. (3) The production of temporary diabetes by injection of anterior pituitary extracts.

The functional activity of the hypophysis, i.e. the rate of formation and release of the various pituitary hormones, is influenced by the secretion of the endocrine glands. This balance is also influenced by the activity of the tissues of the body. An example of the response of the endocrine glands to environmental change is the enlargement of the gonads in animals which have a seasonal breeding period with increased light. After removal of the eyes, gonad activation can be induced in some birds by direct illumination of the hypophysis through a tube leading to that gland!

The review concludes by drawing attention to the importance of the sensitivity of the end-organs upon which the hormone acts. Growth for instance depends on the responsivity of the epiphysial cartilages. Injections of the growth-promoting factor into a dachshund cause growth of the vertebral column, into a collie increase in length of the legs. Likewise in dogs it can be shown that at early ages some of the components of the gonads are unresponsive to gonadotropic hormones; responsivity develops with age. Although the gonadotropic hormones are essential to sexual maturation it would not be justifiable to attribute sexual maturity solely to them; the development of responsivity is also an essential factor. The responsivity of the end-organ thus plays an important part in the acting and the interrelations of the endocrine glands.

THE ANTERIOR LOBE OF THE HYPOPHYSIS IN INTERMEDIARY METABOLISM:

This paper deals with the problems of experimental diabetes and the relation between the metabolic factors of the anterior pituitary and the islets and the adrenals.

STILBOESTROL-INDUCED GYNAECOMASTIA IN THE MALE.

The subject of the experiment was a male sexual criminal, aged 27 years. Assay of his urine showed abnormally high amounts of testicular and gonadotropic hormones. The figures obtained were 285 bird units of androsterone, 30 rat units of androsterone, 20 rat units of oestrogen, and 120 rat units of pregnancy gonadotropic placenta.

He was given orally 5 mgm. of stilboestrol daily for 60 days until a total of 300 mgm. had been given. He was then given 5 mgm. every other day for 36 days. A total of 480 mgm. of stilboestrol was thus given without any evidence of any toxic effect. At the end of 75 days' therapy the breasts commenced to enlarge. Under treatment the penis and testis diminished to two-thirds of the pre-therapeutic size.

### Alleged Hepatotoxic Action of Stilboestrol.

As a test of hepatic function the authors used the bromo-sulphalein retention test, which they consider sensitive to a liver deficiency of clinically significant degrees. Applying the test to a series of menopausal patients no toxic effects were observed even in women with some liver malfunction to begin with. This was true even with doses of 5 to 10 mgm. daily. Furthermore, relatively huge doses of stilboestrol in rats and a dog did not give rise to any gross or cellular lesions of the liver or kidneys. Finally, a man who was recovering from an attack of acute hepatitis was able to take 5 to 10 mgm. daily for 3 weeks without the slightest evidence that his convalescence was retarded.

### Clinical Studies of Stilboestrol.

One hundred and twenty-five women passing through the natural and the surgical menopause were treated for periods of two weeks to six months with stilboestrol in doses ranging up to 60 mgm. In 75 per cent of the cases good results were obtained, 39 per cent of the patients reporting a better response than with other oestrogenic substances used previously.

Forty-two per cent of the patients complained of some untoward symptoms. In the majority of cases nausea and vomiting were the only complaints. Headaches and dizziness rated second in importance. One case of psychotic excitement and two cases of severe diarrhoea occurred. One very sensitive patient had a severe local reaction with vaginal discharge, cystitis, pruritus vulvae and breast enlargement on a total dose of 3 mgm. given by mouth in 0.5 mgm. doses daily. In another patient a galactocele developed.

The authors found 10 to 30 per cent of the stilboestrol was excreted in the urine and the faeces during the first 10 days following its administration.

### Lactogenic and Mammogenic Hormones.

More advance has been made in the chemical study of prolactin than in any other pituitary hormone. It can be crystallized out of extracts as a protein compound. There is evidence that prolactin is formed in the eosinophile salts. Small amounts can be recovered from postpartum urine.

In assessing the clinical value of prolactin it must be borne in mind that lactation involves several hormones and many other factors. The most recent study is that of Kenny and King, who treated 43 women with prolactin. In 74 per cent of the treated women lactation was sufficient, as compared with a figure of 21 per cent in a control group.

Recent work confirms older views that the oestrogen factor of the ovary induces duct growth and an oestrogen-progesterone complex induces

alveolar development. These effects depend upon a normal pituitary function and are not observed in hypophysectomized animals. However hypophysectomy in pregnancy does not affect mammary growth, and there is evidently a placental factor concerned which can replace the hypophysial effect. In young male mice development of the breasts can be accomplished with a wide variety of oestrogens, androgens and with desoxycorticosterone acetate.

### The Antihormones.

The existence of antihormones has been invoked to account for the gradual loss of responsivity to hormone injections, especially those of the pituitary. For instance an antithyrotropic serum can be prepared. This serum shows marked but not absolute species specificity. Although complement-fixing antibodies may appear in the serum of animals treated with hormone extracts nearly all workers agree that there is no parallelism between the immunological titre and the quantity of, say, the antigonadotropic substance physiologically determined. Some observations, however, favour an immunological interpretation or at least suggest the antihormone is formed only under abnormal experimental conditions.

Antihormones have been also described for the adrenal cortex and the parathyroid.

### Dysfunctions of the Anterior Lobe of the Pituitary.

Therapy with pituitary gonadotropic substances is still crude. While chorionic gonadotropin is a factor in sustaining luteal activity in early pregnancy it has no effect on non-pregnant women, in whom the only appropriate substances for stimulating ovarian hypofunction are anterior pituitary extracts and serum from pregnant mares. It is not yet justifiable to assume that mare's serum concentrate provides a complete substitute in human hypopituitarism. To stimulate ovarian function intensive dosage is required. Hisaw suggested this should be done by giving an intravenous injection of a mixture of follicle-stimulating and luteinizing anterior pituitary extracts followed for several days by sustained hypodermic use of the same substances to stimulate the corpus luteum. A complete programme has been also reported by Siegler and Finn with some promise of success. They suggest giving 100 to 300 international units hypodermically for several days to stimulate follicle ripening followed by a single intravenous dose of 1,000 to 1,500 units to initiate ovulation, and the 4 to 6 days more of hypodermic therapy to sustain function in the corpus luteum. Even with the most potent commercial extracts 1 c.c. daily cannot be regarded as a complete replacement for the anterior lobe of the human pituitary.

### Chemotherapy of Gonococcal Infections.

Sulphapyridine was used in 300 cases of gonorrhoea. The cure-rate was 85 per cent for patients not previously treated and 70 per cent for those failing to respond to previous sulphanilamide therapy. No carriers were encountered in patients treated. Larger doses of 6 gm. daily were no more efficacious than smaller doses of 2 gm. daily. Toxic manifestations were significantly less than with sulphanilamide treatment. The authors consider that blood concentration studies had a limited clinical application in sulphapyridine therapy and the total lack of major toxic effects in the group makes it justifiable to dispense with blood counts, haemoglobin determinations and urine analysis, if lack of facilities for these would otherwise curtail the use of the drug.

### Pharmacology of Sulphapyridine and Sulphathiazole.

The sodium salts of these two drugs are absorbed more rapidly than their respective free acids. The glucosides are absorbed from the gastro-intestinal tract less rapidly than the free acids. The simultaneous administration of alkali in the form of sodium bicarbonate or magnesium oxide with sulphathiazole hastens the absorption of the compound. The conjugation of sulphapyridine is greater than that of sulphathiazole. Following the oral exhibition of equal doses the blood concentration of the unconjugated drugs is the same but the total blood concentration of sulphapyridine is the higher.

### Agranulocytosis from Sulphathiazole.

A fatal case of subacute endocarditis treated with sulphathiazole is reported. The agranulocytosis began during the third week of treatment with the drug.

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